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## Original Communications

### X-RAY DIAGNOSIS OF UTERINE PATHOLOGY\*

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THE science of roentgenology was still in the earliest stages of its development when investigators became interested in the possibility of visualizing the uterus and Fallopian tubes. In 1902 Kelling<sup>1</sup> in Dresden suggested that conditions in the abdominal and pelvic cavities might be investigated endoscopically after the injection of gas. The first known attempt to visualize the interior of the uterus occurred in 1909 when Nemenow<sup>2</sup> injected the uterus with Lugol's solution and succeeded in obtaining a roentgenogram of the organ. At that time little attention was paid to his report. Indeed, his work was overlooked in surveys of uterosalpingography published twenty years later. Subsequently, sporadic trials at uterine visualization were made with a variety of radiopaque agents. Rindfleisch<sup>3</sup> in 1910 described his attempt at hysterography with aqueous bismuth paste. Lorey<sup>4</sup> prepared a report in 1912 describing a method of visualizing the Fallopian tubes by injecting isotonic colloidal silver into the uterine cavity. Also unnoticed for a long time was the work of Dartigues and Dimier<sup>5</sup> who in 1913 initiated their investigations on the feasibility of combining periuterine and intrauterine roentgenography for the precise diagnosis of uterine tumors. They injected 10 per cent Collargol solution into the uterus and at the same time an insufflation of the bladder with air was performed to aid visualization of uterine contour. Publication of this work was delayed until 1916. Meanwhile in 1914 Rubin<sup>6</sup> and Cary<sup>7</sup> demonstrated the feasibility of x-ray determination of the presence of tubal patency or occlusion by injection of Collargol into the uterine cavity. As new radio-

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paque agents were discovered each had a trial for delineation of the uterus and adnexa. Some of the many substances used were sodium iodide, sodium bromide, potassium iodide, lithium iodide, barium emulsions and many preparations of thorium. Each of the media injected suffered from some serious drawback. Most proved extremely irritating and fatalities occurred in some cases. Something better was required and this was found for the first time in the use of Lipiodol.

Lipiodol, a 40 per cent combination of iodine with poppy-seed oil, was introduced in France in 1902 as a therapeutic agent for intramuscular injection in systemic conditions where iodine was indicated. It was accidentally observed that the sites of injection continued to appear on roentgenograms for prolonged periods of time. This fact, and the apparent safety of Lipiodol, suggested its use as a radiopaque agent to Sicard and Forestier<sup>8</sup> who reported its epidural and intrathecal injections in 1921 and 1922. Meanwhile, in Argentina in 1921 Heuser obtained roentgenograms of the uterus and Fallopian tubes with Lipiodol injections into the uterine cavity. Heuser called special attention to the value of Lipiodol uterosalpingography for the early diagnosis of pregnancy. Since Lipiodol injection of tuberculous pregnant women did not produce therapeutic abortion he claimed that the agent was safe in this respect. Further, in cases of sterility due to obstruction of the Fallopian tubes, he demonstrated that it was possible to visualize the inner contour of the tubes and so diagnose the site of obstruction. He also found that by repeated injections of Lipiodol the obstruction could be relieved in some nonpatent tubes, with resultant pregnancy. This work was announced through Case<sup>9</sup> at the Third Pan American Scientific Congress at Lima in December, 1924. In France and Great Britain similar work had been in progress and Poitret<sup>10</sup> in 1924 and Forsdike<sup>11</sup> in 1925 described the technique of hysterosalpingography with Lipiodol. With these announcements uterosalpingography became a widely used procedure. As a result, many new iodized oils such as iodized sesame oil, rapeseed oil, olive oil, and peanut oil were utilized. While many gynecologists and roentgenologists continued to use iodized oils, complications and fatalities were reported with their injection. Consequently, uterosalpingographic examinations were applied more conservatively.

With the discovery of aqueous radiopaque media for use in excretory urography a safe quickly absorbable material presented itself for hysterosalpingography. In 1933 Molinengo and Conte<sup>12</sup> reported the use of Abrodil (Skiodan in the United States) in uterosalpingography. This agent did not find wide application until after 1937 when Titus and his co-workers<sup>13</sup> announced its combination with acacia under the name of Skiodan Acacia, a viscous preparation that did not flow too rapidly out of the tubes and yet was nonirritating, quickly resorbed and excreted by the kidney. Uroselectan, or Diodrast as it is better known in the United States, was reported as a medium for uterosalpingography in 1936 by Prevot and Schultz.<sup>14</sup> In order to obtain some of the advantages inherent in oil media, many attempts have been made to render more viscous the several water-soluble media under different trade names.



Some of the agents used to increase the viscosity are acacia, polyvinyl alcohol, methacrylic acid, and carboxymethylcellulose. Procaine has been added to some media to prevent the painful effects of these hypertonic solutions.

The perfect medium for hysterosalpingography is not as yet available. However, for the purposes of hysteroscopy the aqueous radiopaque medium is excellent for visualization of intrauterine pathology with a minimum of complications and discomfort.

Despite the background of forty years of investigation and clinical use, hysterosalpingography is still struggling for proper recognition. Many large gynecological services employ this diagnostic procedure rarely, if at all. The failure to do so can be attributed I believe to two factors, the first a fear of complications and the second a matter of inconvenience. The test is and should be strictly considered a gynecological procedure. However, the x-ray facilities in most hospitals are such that it is difficult for the gynecologist to perform the procedure in the general x-ray rooms. We, however, are fortunate in that the urological x-ray facilities are on the same floor and adjacent to the gynecological wards. The mere physical convenience has made it possible for us to incorporate hysteroscopy as a routine procedure in the diagnostic study of most cases of uterine bleeding and sterility. The test is performed only by the gynecological staff. The x-ray interpretation of the films should also be made by the gynecologist who can correlate the symptoms and physical findings with the radiographic pictures. We have performed over 3,000 hysterosalpingograms with relatively few disturbing complications.

The technique employed for the investigation of intrauterine pathology is simple. The patient is placed in lithotomy position on an x-ray table equipped with a Bucky diaphragm. A bimanual examination is performed to determine the position, size, and mobility of the uterus and to note the presence of any palpable pelvic abnormality. A preliminary film of the abdomen and pelvis is taken. A fiber bivalve speculum is then inserted into the vagina and the cervix exposed and painted with an antiseptic solution. The anterior lip of the cervix is grasped with a tenaculum and a uterine sound introduced into the uterine cavity to note the direction and depth of this structure. The iodized material is injected into the cervical canal by using a syringe attached to an ordinary insufflation cannula equipped with a well-fitting rubber acorn tip. Tight occlusion of the external cervical os is obtained by making pressure against it with the rubber acorn tip. Fractional amounts of opaque material are injected slowly and gently. Films are taken after the injection of 1, 2, or 4 c.c. of dye, depending on the size of the uterus. A film in the oblique position is taken after the last injection. This facilitates the interpretation of filling defects in the uterine cavity and demonstrates lesions on the posterior uterine wall which might otherwise escape detection. We use water-soluble radiopaque media almost exclusively for this procedure with excellent radiographic results.

Indications for hysteroscopy are the following: abnormal uterine bleeding, dysmenorrhea, sterility despite the presence of normal tubal patency, and preoperative investigation prior to myomectomy.

Fig. 1.

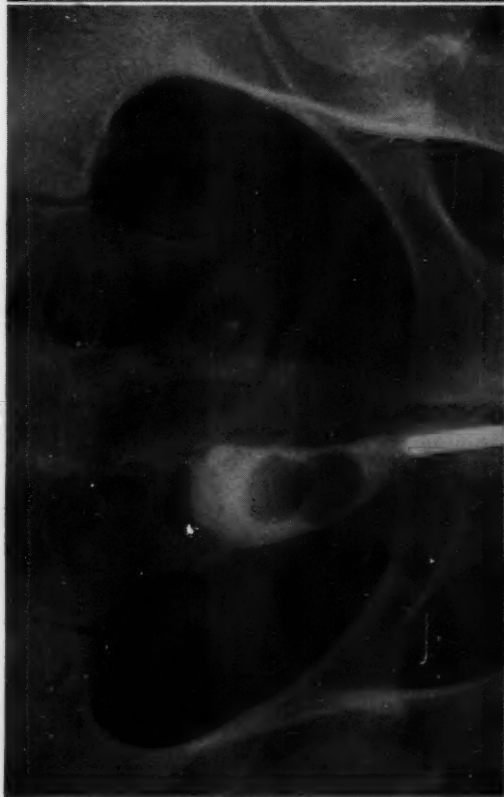


Fig. 2.



Fig. 3.



Fig. 4.



Fig. 1.—Hystero-gram revealing two large endometrial polyps which were removed by curettage.  
 Fig. 2.—Postoperative hystero-gram. Bicornuate uterus with a large endometrial polyp in the right horn.  
 Fig. 3.—Postoperative hystero-gram after curettage and removal of the endometrial polyp.  
 Fig. 4.—Preoperative hystero-gram prior to myomectomy in a young woman demonstrating an elongated and deformed uterine cavity due to a large submucosal myoma.

Contraindications are: acute and subacute pelvic inflammatory disease, intrauterine gestation, cervicitis with purulent discharge, and active uterine bleeding. Hysterography should be deferred if temperature, sedimentation rate, or blood count reveals evidence of inflammatory activity.

The following conditions have been clearly demonstrated by hysterography: (1) endometrial polyps, (2) submucous and intramural fibroids, (3) hyperplastic endometrium, (4) adenomyosis, (5) fundal carcinoma, (6) tuberculous endometritis, (7) congenital anomalies of the cervix and fundus of the uterus, (8) cervical strictures, (9) chronic endocervicitis, and (10) pregnancy and retained secundines.

The most common indication for hysterography is undoubtedly *uterine bleeding*. In our series of more than 3,000 cases about 80 per cent of the examinations were performed to determine the presence of intrauterine pathology. Hysterography is now performed routinely on patients with normal or slightly enlarged uteri and a history of prolonged menorrhagia or menometrorrhagia. Many cases have been seen in which dilatation and curettage have been performed by ourselves and other gynecologists and the operation has revealed no apparent intrauterine lesion. The cause of bleeding has subsequently been revealed by hystrogram to be a small submucous fibroid or polyp completely missed by the curette. In reviewing the cases of our patients over 60 years of age with the complaint of uterine bleeding we found that in 54 per cent the bleeding was associated with benign lesions. In 33 per cent, uterine polyps were the cause of bleeding. Eight patients were over 70 years of age. Submucous fibroid proved to be the cause of bleeding in 12 per cent of this group. Because of these facts we do not limit ourselves in the use of hysterography in the case of the elderly patient. It is of great value in determining the surgical procedure to be employed. A presentation of hystrograms and case histories will clearly demonstrate the value of the procedure.

*Uterine polyps* are found very frequently. They have been demonstrated in girls as young as 15 years, and in elderly women of 76 years. Polyps may vary in size, be single or multiple, or be present in any portion of the uterine cavity. They are usually sharply outlined and do not distort the uterine cavity or produce irregularities of its walls. Fig. 1 demonstrates the various radiological findings in the presence of uterine polyps. Figs. 2 and 3 are especially interesting in view of the fact that this patient had a history of three uterine curettages with no relief of uterine bleeding. The hystrogram revealed the polyp in one horn of a bicornuate uterus. Curettage was then done, and not terminated until the polyp was removed. The postoperative hysterography revealed the absence of the polyp and the menorrhagia ceased.

Although *submucous myomas* form only a small percentage of uterine myomas, they are important clinically. They impinge upon the endometrium or may actually lie pedunculated within the endometrial cavity. Due to this fact they can cause severe uterine bleeding and dysmenorrhea. Submucous fibroids, if small and unassociated with other fibroids, are in most instances difficult or impossible to diagnose by palpation. It is in these cases that hys-

Fig. 5.

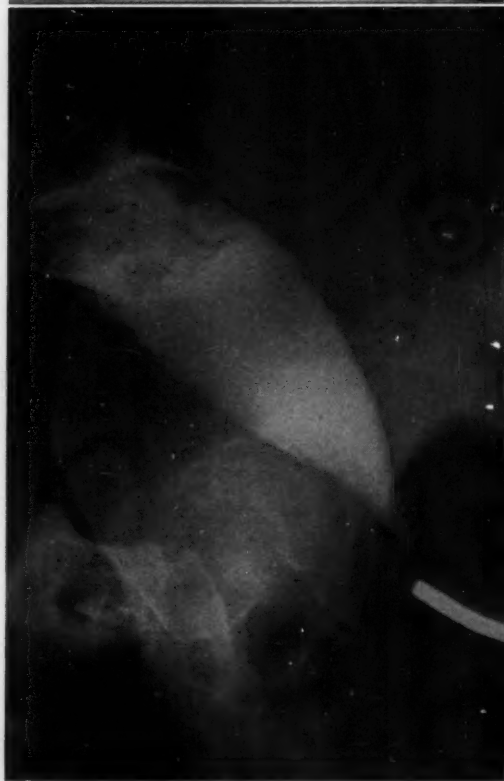


Fig. 6.



Fig. 7.

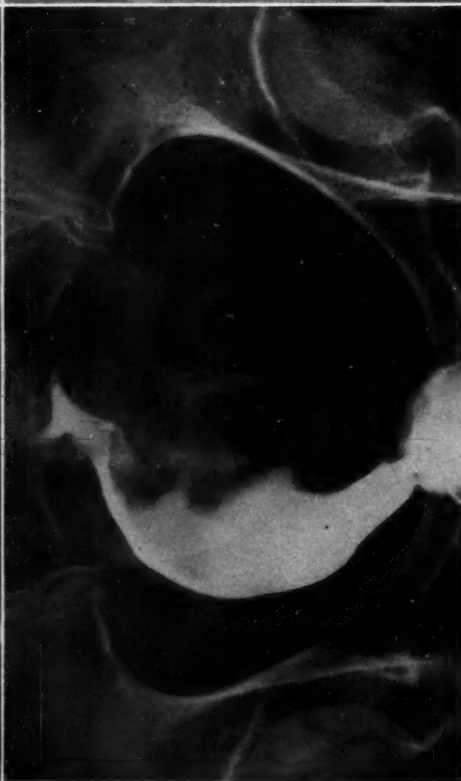


Fig. 8.



Fig. 5.—Preoperative hystero-gram revealing a markedly enlarged uterine cavity with multiple filling defects in its upper third. At myomectomy sixty-three fibroids were removed.

Fig. 6.—Preoperative hystero-gram in a patient with an unenlarged uterus. The diagnosis of a submucous fibroid is made by the globular appearance of the endometrial cavity despite the fact that the fibroid is overshadowed by the radiopaque medium.

Fig. 7.—Demonstration of a large cervical fibroid in a 63-year-old woman. There is marked elongation and deformity of the cervical canal and a tiny atrophic uterus is seen surmounting the cervical fibroid.

Fig. 8.—Hystero-gram revealing a normal-sized uterine cavity filled with uterine polyps. Pathological diagnosis: endometrial hyperplasia.



terography is a great diagnostic aid. Submucous fibroids may be single or multiple and vary greatly in size. They may enlarge and distort the uterine cavity in many ways. A small intramural fibroid just beginning to develop a submucous component will produce only slight distortion along one border of the uterine cavity. On the other hand, large intramural fibroids may develop submucous components which produce great distortion and elongation of the endometrial cavity (Figs. 4 and 5). A pedunculated or sessile submucous fibroid in an unenlarged uterus produces a typical globular uterine cavity (Fig. 6). An occasional submucous fibroid may be so small that it cannot be differentiated from a polyp.

*Intramural myomas* in the cervix may produce distortion of the cervical canal. If small they may just produce a curved instead of straight canal. If large the cervical canal may become greatly elongated. Fig. 7 demonstrates the deformity caused by a large cervical myoma in a 63-year-old woman. Surmounting the large cervical fibroid is visualized the cavity of a small atrophic uterus.

When myomectomy is contemplated because of palpable fibroids producing sterility or abnormal bleeding, hystero-graphy is performed to reveal the presence of submucous fibroids or polyps. The absence of either of these intrauterine growths obviates the routine exploration of the uterine cavity at operation.

The roentgenological appearance of the uterine cavity in the presence of *hyperplasia of the endometrium* depends upon the degree of proliferation. The gross pathological appearance of hyperplasia of the uterine endometrium varies from a minimal hyperplasia, hardly noticeable in the gross specimen, to the most pronounced cases in which the endometrium is greatly thickened and polypoid growths fill the entire cavity of the uterus (Fig. 8). In the presence of a moderate or marked degree of hyperplasia without polyp formation, the x-ray will show the uterine cavity to be either normal in size or slightly enlarged. The borders of the x-ray shadow are hazy due to the prominent folds of the endometrium while the central area shows a uniformly dense shadow without filling defects (Fig. 9).

The radiographic appearance of *adenocarcinoma of the uterus* depends upon the extent of the endometrial surface involved. In the more advanced carcinoma the x-ray shadow will show distortion of the cavity with irregularity of its borders. There is usually a mottled defect with feathery irregular borders (Fig. 10). In early localized lesions, a small irregularity along one border of the cavity with a feathery edge is characteristic. There are cases, however, where carcinoma of the uterus begins with a single polypoid growth and if ulceration has not begun the x-ray appearance cannot be differentiated from that of an ordinary benign polyp. In adenocarcinoma of the cervix, the x-ray outline of the cervical canal may show irregularities protruding into it or an irregular excavation along one or both borders. In the series reported, one case of sarcomatous degeneration of a submucous fibroid was found and the hystero-gram showed a large distorted round uterine cavity with a markedly

Fig. 9.



Fig. 10.



Fig. 11.



Fig. 12.



Fig. 9.—Hystero-gram demonstrating endometrial hyperplasia. The thickened endometrium produces a hazy border surrounding a uniformly dense shadow in the center of the uterine cavity.

Fig. 10.—Hystero-gram demonstrating adenocarcinoma of the uterus. The filling defects on the left side of the uterine cavity are irregular and have feathering borders.

Fig. 11.—Hystero-gram in a case of sarcomatous degeneration of a submucous fibroid producing a large round uterine cavity with a mottled irregular radiopaque shadow.

Fig. 12.—Adenomyosis. The above uterine cavity is normal in size but the short tubelike and saccular projections are characteristic of adenomyosis.

mottled irregular x-ray shadow. The hystrogram in this particular case did not resemble any other seen in the series of carcinomas found by hystero-graphy (Fig. 11). The use of hystero-graphy should in no way be considered a substitute for curettage. However, careful fractional injection of radiopaque material into the uterine cavity under low pressure is probably less traumatic than the surgical curettage. Swedish gynecologists use hystero-graphy extensively for diagnosis of adenocarcinoma of the uterus and report large series of cases detected by this procedure.

Many patients present themselves complaining of menorrhagia associated with varying degrees of *dysmenorrhea*. The palpable findings may reveal a uterus normal in size or slightly enlarged. Dilatation and curettage usually show no gross abnormalities. In a large number of these patients the menorrhagia and pain persist and the presumptive diagnosis is adenomyosis. Hystero-graphy may be a great aid in establishing the diagnosis accurately. In such patients the hystrogram may reveal a rather characteristic shadow. The uterine cavity may appear normal in size, or somewhat enlarged. Short spicule- or tubelike projections extend outward from its borders and many of them end in tiny saccules (Fig. 12). This is due probably to irregular invasion of the endometrium into the adjacent uterine musculature. Adenomyosis may exist deeper in the uterine musculature without connection to the uterine cavity and in these cases the hystrogram will not reveal the findings described. When, however, these x-ray findings were present and hysterectomy was performed the micropathological findings were those of adenomyosis.<sup>15</sup>

*Tuberculous endometritis* is not a common entity in this area. In the Near Eastern countries, however, the condition occurs frequently and is a common cause of sterility. We have seen 3 such cases in our sterility clinic and hystero-graphy revealed a narrowing of the cervical canal and a slightly enlarged uterine cavity. The x-ray shadow of the uterine cavity revealed numerous irregular, hazy, smudged defects (Fig. 13). In one case both the cervical and uterine canals were narrowed.

The x-ray appearance of *cervical fibroids* and *endocervical fibroids* has already been discussed. Two additional conditions, however, can be diagnosed by x-ray. These are chronic endocervitis and cervical stricture. In chronic cervicitis the cervical canal appears widened and bulbous. The walls present a serrated appearance resembling in some degree an inverted Christmas tree (Fig. 14). In the presence of cervical stenosis the cervical canal appears as a very thin shadow which may be elongated and sometimes tortuous. The uterine cavity itself may appear normal in size or small in the presence of an infantile uterine body (Fig. 15).

*Early pregnancy* and *retained products of conception* may produce x-ray shadows that are somewhat bizarre and confusing. In early pregnancy the hystrogram reveals the uterine cavity usually enlarged and globular in outline and containing a filling defect due to the presence of the amniotic sac. This picture may resemble that of a submucous fibroid. In the presence of retained secundines, the x-ray shadow will differ depending upon the amount of retained

Fig. 12.—Adenomyosis. The above uterine cavity is normal in size but the short tubelike and saccular projections are characteristic of adenomyosis.

Fig. 13.

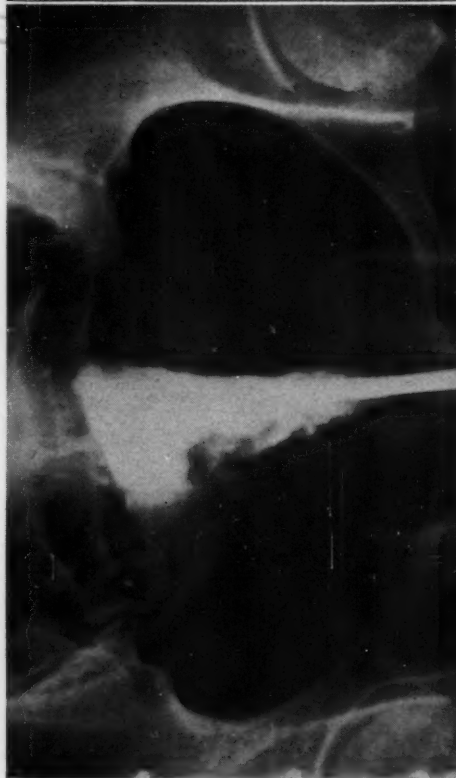


Fig. 14.



Fig. 15.



Fig. 16.



Fig. 13.—Tuberculous endometritis producing irregular hazy defects in a normal-sized uterine cavity.  
 Fig. 14 —Hystero-gram demonstrating a dilated cervix with serrated borders due to chronic endocervicitis. A small polyp is present along the right border of the uterus.  
 Fig. 15.—Hystero-gram showing cervical stenosis. The cervical canal is elongated and very narrow.  
 Fig. 16.—Hystero-gram of a uterus didelphys. There is a defect in the shadow of the right uterus due to cavity of a small ante-flexed over by curettage.



placental tissue and coagulum present. The cavity may or may not be enlarged but within it there will be filling defects which are irregular and bizarre in shape. The appearance is such that at times it is difficult to differentiate it from that of fundal carcinoma.

To develop into a normal uterus the two Müllerian ducts must meet in the midline. Their size and growth must be equal. They must contact each other and the duct walls must fuse. After this fusion the uterus becomes a single organ by the involution of the septum which resulted from the fusion of the two ducts. *Congenital anomalies of the uterus* may occur when the process of development and fusion of the Müllerian ducts is not complete. Certain uterine malformations are evident on pelvic examination. In these cases hysterosalpingography is indicated to determine the degree of maldevelopment. On

Fig. 17.



Fig. 18.

Fig. 17.—Hystero-gram revealing extravasation of the radiopaque material into the uterine and pelvic vasculature.

Fig. 18.—Extravasation of radiopaque medium into the pelvic vasculature without visualization of the uterine cavity. The same phenomenon occurred on three different attempts at hystero-gram.

the other hand, there are many cases in which malformations of the uterus can be demonstrated only by hystero-graphy or at the time of operation. Our diagnosis of uterine anomalies has become more frequent since the use of hystero-graphy. The following conditions have been demonstrated in our series: uterus didelphys (Fig. 16), uterus bicornis duplex, uterus bicornis unicollis, uterus septus duplex, uterus subseptis, uterus arcuatus, and uterus unicornis. Many patients with these anomalies present themselves because of sterility. Hysterosalpingography gives us an accurate picture of the extent of the pathology and in this way some clue as to prognosis and indications for corrective surgery.

### Discussion and Summary

In 2 per cent of the patients examined by hysterosalpingography there was extravasation of the opaque medium into the uterine and pelvic vascular system. Since the medium we employ is water soluble and similar to that used for intravenous pyelography there was no untoward reaction in any of these patients. In one patient who complained of severe dysmenorrhea and menorrhagia, intrauterine injection of the medium under low pressure on three different occasions revealed the dye outlining the pelvic vascular tree without adequate filling of the uterine cavity. The extirpated uterus in this case showed a diffuse adenomyosis. The degree of extravasation may be slight or it may demonstrate almost the entire vasculature extending as high as the renal veins (Figs. 17 and 18).

Untoward reactions to the investigation of the uterine cavity with water-soluble media are very infrequent. It is only when large amounts of the opaque medium are employed for outlining the Fallopian tubes that one encounters pain due to spill of the medium into the peritoneal cavity or due to distention of the uterus and tubes under higher pressure. The use of water-soluble media obviates the disadvantages of Lipiodol and other oil media. Embolization and residual granulomas in the Fallopian tubes and peritoneal cavity do not occur since there is rapid and complete absorption of the water-soluble dyes. Phenomena from an allergy to the medium employed have occurred in very rare instances and have been easily controlled with antihistaminics and sedation. Pelvic inflammatory reactions are rare. These have occurred in our series only when investigations for sterility were being conducted and a sub-acute or chronic salpingitis was reactivated.

Hystero-graphy is a simple and safe diagnostic procedure and the gynecologist should not hesitate to use it. It has been a great aid to us in determining the choice of therapeutic measures.

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### Discussion

DR. WILLIAM E. STUDDIFORD.—Hysterography appears to be a method which is valuable in the diagnosis of many conditions. There is one group of cases, however, in which the use of the hystrogram should be a matter of concern. Although, in recent years, it has been shown that carcinoma of the corpus spreads through the lymphatics in a certain proportion of cases, in most instances this cancer spreads by retrograde extension backward through the tubes to produce ovarian and peritoneal metastases. The use of the hystrogram in such cases would seem to favor the production of metastases. When bleeding is present in patients above 40 years of age, I believe a hystrogram is contraindicated until the presence of malignancy of the corpus or cervical canal have been eliminated by other diagnostic methods.

I would also like to know the exact proportion of abnormalities discovered in this large series of 3,000 cases. To put it differently, what proportion of the series were found to have normal uteri?

DR. LOCKE L. MACKENZIE.—I should like to reinforce what Dr. Studdiford has just said concerning the performance of a hystrogram if malignancy is suspected. In the 7 cases of adenocarcinoma which Dr. Davids showed us there were 2 and possibly 3 in which the tubes were outlined. I should like to mention briefly one case from the Service at the University Hospital. A hysterosalpingogram was done upon a 50-year-old patient, and a diagnosis of polyp of the endometrium was made. She was requested to enter the hospital but did not return for a period of four or five months. On this second visit, masses were evident throughout the pelvis, and upon operation metastases to the tubes and ovaries on both sides were found. We felt we had definitely made a mistake in introducing a contrast medium into this uterus. It is true that we generally use more dye than Dr. Davids does—10 c.c. instead of 4. However, we have come to the conclusion that a diagnostic curettage is safer than is any x-ray procedure, using a contrast dye in the uterus, when the possibility of carcinoma of the fundus exists.

DR. MORRIS A. GOLDBERGER.—We have had a great deal of help in the diagnoses of intrauterine lesions by hysterography. As you heard from Dr. Davids' report, we have done it in over 3,000 cases and we have had very few complications, particularly where just the hysterography was done. We try to use a very small amount of opaque fluid, usually from 2 to 4 c.c. In fact, rarely are 5 c.c. introduced into the uterus as the syringe is rarely filled to more than the 5 c.c. mark.

I do not think that Dr. Davids wanted to convey the impression that we are using hysterography for the diagnosis of intrauterine carcinoma. In the hystero grams shown it was discovered in unsuspected cases where the only symptom was irregular uterine bleeding.

Before any patient with a history of uterine bleeding is submitted to hysterography, a Papanicolaou smear is made. If the Papanicolaou smear is negative, and there is no palpable pathology, we resort to hysterography to rule out a polyp or submucous fibroid. It is a great help to know that you have a polyp in the right or left horn of the uterus so that when you insert the ring forceps into the uterus, you will come out with the polyp

every time. If you curette blindly without hystero-graphy you may curette all around a polyp or submucous fibroid. We have had it happen to us and we have seen cases from other institutions that had repeated curettage without hystero-graphy. With the aid of hystero-graphy the polyp is located and may be removed, almost as easily as under vision.

DR. HENRY S. ACKEN, JR., Brooklyn, N. Y.—May I ask Dr. Goldberger whether he thinks the Papanicolaou smear is a sufficient evidence for the absence of endometrial carcinoma? I recall at least three instances in which the Papanicolaou smear was negative and yet the patient had an endometrial carcinoma. I would agree that for cervical carcinoma the reliability is considerably greater.

This paper offers us a great deal to think about and certainly in those patients who have had curettage and in whom the diagnosis has not been established, this procedure might well lead us to a correct diagnosis.

DR. GOLDBERGER.—We do endometrial aspiration for our Papanicolaou preparations in addition to the vaginal smear. That is why we feel confident about it.

DR. MORTIMER D. SPEISER.—May I ask what the interval is between the hystero-graphy and any subsequent intrauterine manipulation?

DR. R. GORDON DOUGLAS.—I would like to ask Dr. Davids if he would tell us just what patients he thinks should be subjected to this diagnostic procedure. For instance, should all patients with functional bleeding undergo the procedure? Does your experience indicate that this diagnostic method is more accurate than careful exploration of the uterus with a sound or curette?

DR. DAVIDS (Closing).—In answer to Dr. Studdiford, we do not assume that this is the diagnostic procedure of choice for carcinoma of the fundus. On the other hand, in the Scandinavian countries many gynecologists and radiologists feel that hystero-graphy done carefully, with injection of 2 to 3 c.c. of medium, is less traumatic than a diagnostic curettage.

In reply to the question as to whether the x-ray diagnosis is sufficient for us to carry out definitive therapy for carcinoma of the uterus, the answer is No. We do a diagnostic curettage in addition before we submit a patient to surgery or radiation therapy.

I cannot give Dr. Studdiford the exact percentage of cases of the entire series in which abnormalities were found by the x-ray. I have the impression that in about 30 per cent of the cases pathology was found and surgery indicated.

The 15-year-old girl who was subjected to hystero-graphy had previously had a diagnostic curettage for intractable menorrhagia at another institution. The menorrhagia persisted and a hystero-gram was performed without any difficulty. A large polyp was visualized in the uterine cavity and this was removed by us at a subsequent curettage. We have had a number of such cases in other young girls 17 to 18 years of age.

The interval between hystero-graphy and operative surgery was in most cases 24 to 48 hours. In one series of cases we used methylene blue in the radiopaque medium and hystero-graphy was performed on the morning of the contemplated surgery. We did this in a group of cases in which we performed a thorough curettage prior to hysterectomy to determine how much endometrium was left in situ after the curettage. In many of the cases in which the opaque medium passed through the tubes we found a small collection of serous fluid in the pelvic cavity probably due to a little irritation of the peritoneum.

In reply to Dr. Douglas' question as to the type of patient subjected to hystero-graphy in the outpatient clinic, I may say briefly that they are patients complaining of irregular or profuse uterine bleeding in whom no obviously palpable fibroids are felt. To rule out the presence of a small submucous fibroid or uterine polyp these patients are sent from the outpatient department to the cystoscopy room, which I described in the text, and hystero-graphy is performed by a member of the gynecological staff. As I said, in 80 per cent of the cases we are not interested in tubal pathology so that 2 to 4 c.c. of the medium



is injected. No preliminary sedation is required for pain since with small amounts of medium there is usually no pelvic spill. Hysterography has been a great aid in these particular patients in determining whether or not they will require admission to the hospital for surgery and whether a curettage or more radical surgery such as myomectomy or hysterectomy will be necessary. With this knowledge the patient can plan or arrange much better for her absence from home or her place of employment.

With the advent of the Papanicolaou smear, the patients have had such tests performed before being sent to x-ray for hysterography.

In carcinoma of the fundus, most cases have been picked up accidentally. On the other hand, as stated in the paper, over 50 per cent of our cases of postmenopausal bleeding were due to benign conditions and we still resort to very careful injection of 2 to 3 c.c. of radiopaque medium into the uterus. In many of these cases hysterography reveals a submucous fibroid and we do not have to subject such a patient to a preliminary curettage. Hysterectomy could be performed without further delay, saving hospitalization time as well as a preliminary surgical procedure. In those cases where carcinoma was found I do not believe that the procedure endangered the patient. With the use of small amounts of dye the spill into the Fallopian tubes will occur very infrequently.

## A CLINICAL STUDY OF PREMENSTRUAL TENSION\*†

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PREVIOUS studies have indicated that premenstrual tension is the result of an estrogen-progesterone imbalance due to deficient progesterone secretion.<sup>1, 2</sup> The consequent uninhibited premenstrual rise in estrogen displays its activity by stimulating increased epithelial proliferation in the breasts and pelvic organs; by altering electrolyte and water metabolism to allow increased retention of extracellular tissue fluid; and by altering carbohydrate metabolism to permit increased sugar tolerance. The hypoglycemia is a recent and striking finding in premenstrual tension.<sup>2, 3</sup> It is clinically manifested by increased appetite or a craving for sweets, and a trembling of the hands described by the patients as the "shakes." The psychic manifestations as well as the weakness and fatigue are also largely ascribed to the hypoglycemia.

The present clinical study, prompted by the above findings, was conducted at Westfield State Farm, a state prison and reformatory for women at Bedford Hills, N. Y. The objectives of the study were: (1) to determine the incidence and severity of the premenstrual symptoms; (2) to determine the effect of premenstrual tension on social attitude, behavior, and work output; (3) to correlate any possible connection between the time of the commission of the crime for which the inmates were imprisoned and the phase of the menstrual cycle; (4) to evolve, if possible, an effective therapy for the relief of the premenstrual distress.

### Materials and Methods

The subjects of this experiment were volunteers from the inmates of the Westfield State Farm, New York. Approximately 50 per cent of the volunteers were Negro and 50 per cent white women. The volunteers were from 21 different counties in New York, but about 60 per cent of the participants came from the metropolitan area of New York City. The general socioeconomic background of the subjects was low.

Inmates who were going through or had passed the menopause were not included in the study. Known drug addicts whose menstrual periods were disturbed (most addicts do not menstruate while taking narcotics) were also excluded from the study. Since those judged criminally insane are not sent to Westfield State Farm, it is assumed that in general none of the subjects

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†This study was supported in part by a grant from the National Dairy Council, Chicago, Ill.

was psychotic. The participants were literate and within acceptable ranges of normal and low-normal intelligence (there were no known feeble-minded participants). Those subjects who were paroled or released during the period of investigation, those who were dropped at their own request, and those who did not complete the regime required by the experimental design were also eliminated from the study. All subjects were ambulatory and without obvious physical defects.

The inmates volunteered for participation in the survey with the understanding that they were free to withdraw at any time without incurring official displeasure. The subjects were not given any special consideration or inducements by the administrative authorities as a reward for participation in the experiment.

Westfield State Farm is a highly progressive institution divided into two sections, a prison and a reformatory which are separated by a main highway. The total population of these subdivisions combined fluctuates around 600 inmates with approximately 250 in the prison and 350 in the reformatory.

The women in the prison serve sentences up to life for grand larceny, burglary, felonious assault, manslaughter and murder, and other similar offenses, while the younger group in the reformatory serve sentences up to three years as wayward minors, prostitutes, narcotic addicts, and for offenses such as petty larceny, assault, bigamy, and neglect of children.

Two hundred forty-nine volunteers were included in the current study. These constituted 51 per cent (131 subjects) of the prison population and 33 per cent (118 subjects) of the reformatory population. The current study covered a period of three months. The average age of the volunteers from the prison was 32.4 years, with the range from 18 to 53, and the average age of those from the reformatory was 21.4, with a range from 16 to 31.

### Plan of Procedure

Volunteers for the study were given a self-rating scale of 21 items which reflect nervous and emotional tension, symptoms due to hypoglycemic reactions, water retention, and disturbances in menstruation. The volunteers were requested to "Please circle the appropriate word beside each symptom that may be present during the days preceding the menstrual period." Symptoms were rated as "none," "mild," or "severe."

The subjects were divided into four experimental groups, two in the prison and two in the reformatory. In both the prison and the reformatory one of the groups was given oral medication and the other was given a placebo.

The medication\* consisted of an enteric-coated tablet containing various ingredients. This combination has been effective in relieving distressing symptoms in the premenstrual period due to the diuretic effect of ammonium chloride,<sup>4</sup> the antispasmodic effect of the homatropine methylbromide, the mildly stimulating effect of caffeine, and the dual effect of vitamin B complex in increasing the breakdown of estrogens by the liver<sup>5</sup> and by increasing the utili-

\*The medication, Pre-mens, was donated by the Babylon Pharmaceutical Co., Inc., P.O. Box No. 226, Lenox Hill Station, New York 21, N. Y.

zation of proteins. Two tablets were taken three times daily for 10 days preceding the expected onset of the menstrual flow and discontinued with the onset of menstruation. The placebos, identical in external coating and features to the medicated tablets, were taken in the same way.

Because of the known value of a relatively high-protein diet with frequent feedings in hypoglycemia, the prison groups in addition were given a supplementary diet of milk and cheese. This consisted of 5 ounces of homogenized whole milk and  $\frac{1}{2}$  ounce of American, pimento, or Swiss cheese between meals and before retiring. Table I indicates the design of the experiment.

TABLE I. DIVISION OF INMATES INTO EXPERIMENTAL GROUPS

GROUP	DIVISION	NUMBER	TREATMENT	DIET
I	Reformatory	56	Placebo	Regular diet with no supplementary feedings
II	Reformatory	62	Medication	Regular diet with no supplementary feedings
III	Prison	64	Placebo	Regular diet plus supplementary milk and cheese
IV	Prison	67	Medication	Regular diet plus supplementary milk and cheese

It was advised that the salt and sugar intake be minimized during the second half of the menstrual cycle. Salt\* and sugar† substitutes were permitted ad libitum. No supplementary feeding or manipulation of the diet of the reformatory groups was attempted.

Daily weights,‡ work output, and social behavior ratings of the participants in the prison groups were recorded whenever possible by the state employee assigned to this experiment and by the prison staff.

Glucose tolerance tests and vaginal smears were done premenstrually before and after one course of treatment on two groups of subjects randomly selected. There were 12 subjects in the glucose tolerance tests and 14 in the vaginal smears study. The subjects were from both the prison and reformatory in equal numbers.

Six weeks after the first administration of the self-rating scale of premenstrual symptoms, a second form was distributed. The second form duplicated the first, with additional questions which asked the subject to indicate:

- (a) whether she thought her symptoms had changed since the treatment, and
- (b) whether or not she benefited from the treatment.

Since the reformatory groups were far less cooperative than the prison groups, the experiment was discontinued in the reformatory after the second survey. The lack of cooperation in the reformatory may have been due to the

\*The salt substitute, Neocurtasal, was donated by Winthrop-Stearns, Inc., New York, N. Y.

†Sugar substitutes were Sucaryl Sodium donated by Abbott Laboratories, North Chicago, Ill., and Saxin, donated by Burroughs Wellcome & Co., Inc., Tuckahoe, N. Y.

‡Scales used in the study were donated by the Detecto Scales Co., Brooklyn, N. Y.



high percentage of adolescents among the inmates, their shorter sentences, and their apparent nonconformist attitude. These general attitudes were well known and were not restricted to the current experiment.

The participants in the prison who had been taking the placebos and who wished to continue in the study were now put on the medicated tablets. At this time the supplementary feedings were discontinued for the prison groups.

### Results of Experiment

*Incidence of Premenstrual Tension.*—Table II gives the reported incidence of premenstrual tension symptoms of 249 inmates from both the prison and the reformatory who filled out the first rating form circulated. The items of the rating scale are ranked approximately in the frequency of reporting, with an occasional clustering of symptoms.

From an inspection of Table II, the hypothesis of widespread prevalence of periodic emotional tension seems well grounded. The high frequency of nervous and emotional symptoms is remarkably close to the percentage of inmates who reported that their symptoms subsided during or after the menstrual period and then recurred monthly.

TABLE II. REPORTED SYMPTOMS OF PREMENSTRUAL TENSION

SYMPTOM	TOTAL PERCENTAGE	% PRISON	% REFORMATORY
Nervous and emotional instability	84	82	87
Irritability	63	61	65
Nervousness	55	50	59
Fatigue and exhaustion	40	27	54
Crying spell or "blues"	42	45	39
Inability to concentrate	20	16	23
Craving for sweets	37	31	45
Increased appetite	23	16	31
Weakness or faintness	27	24	30
Trembling of fingers (shakes)	27	21	33
Low abdominal pain	70	60	82
Abdominal bloating	50	46	55
Headaches	59	65	53
Generalized aches and pains	43	37	49
Gain in weight or edema	28	30	27
Painful swelling of breasts	28	28	27
Nausea or vomiting	19	14	25
Menstrual disturbance	48	34	64
Symptoms recur monthly	80	81	77
Symptoms subside with onset, during, or after menstruation	83	82	85
Total patients	249	131	118

A tabulation of the number of reported severe symptoms over the age range of the prison volunteers tends to indicate that symptoms are reported with greater frequency by the women in the age ranges of 20 to 30 and 40 to 50 than in the 30 to 40 year range (Table III). In this tabulation no attempt was made to distinguish between types or clinical significance of symptoms. These data contribute to the finding that the reformatory groups, composed of younger women, tended to report more symptoms than the prison participants of the survey.

**Oral Glucose Tolerance Curves.**—The median oral glucose tolerance curve during the premenstrual period of twelve subjects showed a low or flat curve indicating increased tolerance (Fig. 1). At the end of the fourth hour the three subjects with the lowest values (41, 45, and 54 mg. per cent) gave evidence of pronounced hypoglycemic reactions. Also, at the end of the fourth hour only four levels had risen to 80 mg. per cent.

**Vaginal Smears.**—The vaginal smears of 14 volunteers consistently showed evidence of hyperestrogenic stimulation. This was evidenced by the increased number of cornified cells. Although nuclear changes which have been considered as comparable were present, the actual increased cornification was deemed necessary for this diagnosis (Fig. 2).

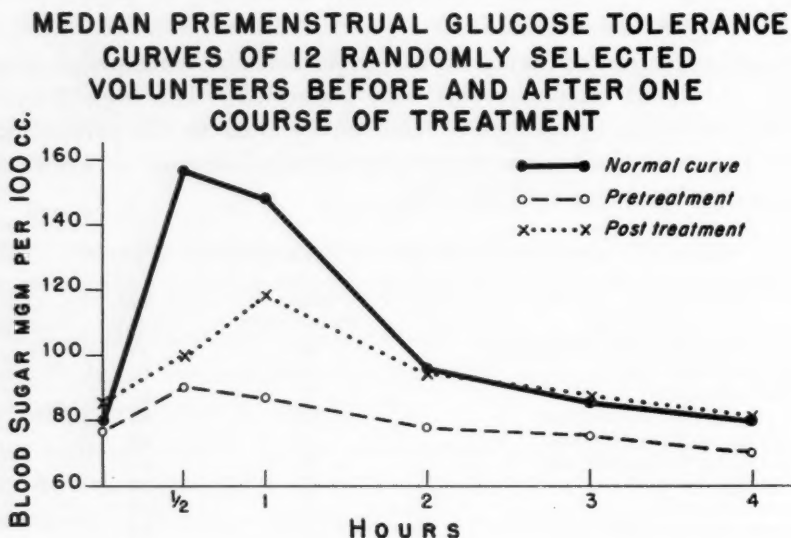


Fig. 1.

A repetition of the oral glucose tolerance curve and the vaginal smears (after a period of medication and during the following premenstrual period) indicated that therapy, while mitigating or alleviating the symptoms, did not markedly alter the underlying pathological findings. Only slight improvement was interpreted in the sugar tolerance curve and practically none in the vaginal smears. Further studies are needed to confirm or negate the clinical impression gained in this study that two or three months of therapy may diminish requirement for treatment for several ensuing months.

**Value of Treatment.**—Interviews with both the inmates and the staff of the prison indicated that the period of research was marked by a definite increase in the morale of the inmates. This observation was of particular interest because the experiment was conducted under adverse conditions: (a) marked overcrowding due to the largest population in the history of the prison, and (b) the time, which was toward the end of the winter when tension was unusually high due to the prolonged indoor restriction. Even those who reported that the experimental regime did not noticeably help *them* were aware

of the rise in general morale and apparent beneficial effect of the medication on the *other* participants of the study. It was reliably reported that some of the prison matrons were so impressed with the visible morale improvement that they also took the tablets which, in some instances unknown to them, were placebos.

*Medication.*—The effect of the medication may be estimated by comparing the reported symptom changes in both the prison groups and both the reformatory groups (Table IV). In the prison, of the 68 who started the medication 5 dropped out and 79 per cent of the remaining subjects reported improvement from the medication, while 21 per cent reported no change or worse symptoms. The control group in the prison who received the placebo had

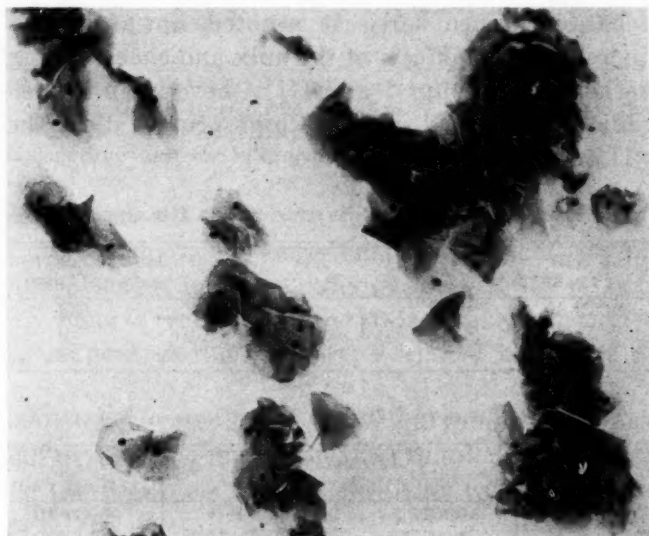


Fig. 2.—Typical vaginal smear taken in the late premenstrual period indicates hyperestrogenic stimulation.

2 of its 64 number drop out of the experiment and 39 per cent of the subjects reported symptom improvement while 61 per cent reported no change or worse symptoms. The probability of a difference as large as this (40 per cent) between these two groups occurring by chance is less than one in a thousand.

Similarly, in the group which received the medication in the reformatory, of those who continued in the survey 61 per cent improved and 39 per cent reported no change or worse. The group which received the placebo in the reformatory reported 15 per cent cases of improvement with 85 per cent of the subjects indicating no change or worse symptoms. This difference (46 per cent) in these two reformatory groups confirms the findings of the prison group at a significant level which could occur by chance variation less than once in a thousand times. Thus it may be concluded that the medication had a significant effect as reflected in the reports of improvement of premenstrual tension symptoms.

*Value of the Milk and Cheese Supplementary Diet.*—The significance of the supplementary diet is indicated by computing the probability of the occurrence by chance of the difference in improvement of the groups which were given the placebo in the prison and the reformatory. The differences between these two groups could occur by chance only between 2 and 5 per cent of the time. The reformatory group (Group I) which had the placebo reported only 15 per cent improvement, while 39 per cent of the prison group (Group III) reported improvement. Consistent with the general effect of the milk plus medication is the finding that in the prison (Group IV) 79 per cent of the participants reported improvement, while only 61 per cent of the reformatory (Group II) reported improvement under medication alone. Whether or not there is an interaction effect of the high-protein diet and the medication which would further facilitate improvement more than merely the sum of their individual effects cannot be determined here. It is noted, however, that while there is a 24 per cent increase in the effects of the milk and cheese diet with the placebo (the difference between Groups I and III), there is an 18 per cent improvement when medication is used with the high-protein diet (the difference between Groups II and IV).

TABLE III. SEVERE SYMPTOMS BY AGE GROUPS

AGE (YEARS)	PERCENTAGE REPORTING 3 OR MORE "SEVERE" SYMPTOMS
19-30	38
31-40	29
41-50	33

TABLE IV. INMATES' REPORT OF EFFECTS OF TREATMENT

EFFECTS	REFORMATORY (USUAL DIET)		PRISON (HIGH PROTEIN, LOW SALT)	
	GROUP I PLACEBO	GROUP II MEDICATION	GROUP III PLACEBO	GROUP IV MEDICATION
Feel "better"	15%	61%	39%	79%
"No change" or "worse"	85%	39%	61%	21%

*Note.*—These percentages are computed on the basis of the number of inmates in each group who completed the treatment regime for one month.

*Value of the Placebo.*—Although the percentage (15 per cent) of the subjects reporting improvement in the reformatory group who received the placebo is not statistically significant, there is a weak suggestion in this datum that some of the emotional components of premenstrual tension will respond to treatment by placebos. This finding is consistent with other investigators' reports but it is surprising that the effect of the placebo alone was not greater.

*Work Output.*—The prison laundry work during the period of the survey was increased almost one-third without an increase in inmates assigned and without noticeable disruptive effects on the girls working there. In other sections of the prison such as the wards, sewing room, nursery, farm, beauty parlor, or kitchen, the work output could not be readily assayed. The completion and opening of a new industry building during the study made the work records invalid for analysis.



*Disciplinary Effects.*—During the period of the survey none of the participants taking the medication required isolation from the general population because of behavioral difficulties, as had been the case previously. A decrease in loss of privileges for lesser infractions of regulations was also noted.

*Dispensary Visits.*—An analysis of the clinic records of the prison indicated that there was a slight decrease in the requests for analgesics and sedatives during the period of the experiment. Table V shows the medication records for both the prison and the reformatory.

TABLE V. DISPENSARY VISITS, JANUARY TO MAY, 1952

	NO. OF VISITS
January	700
February	754
March	663
April	796
May	908

The medication was given to the experimental groups in the prison and in the reformatory during the month of March. It was finally discontinued in the reformatory in April, but continued in the prison until May. The effect of this medication is seen in March, when approximately one-fourth of the total population was taking it.

*Behavior and Attitude.*—The behavior records kept by the matrons were of such varied quality that no general analysis of them was possible. However, marked improvement in many individual cases was reported. The summary of the daily reports recorded by the state employee assigned to this study indicated that "in general the girls were relaxed and were sleeping better than before."

*Daily Weights.*—The recorded daily weights indicated an average gain in the premenstrual period of 3 pounds in the group on placebos and a little less than 1 pound in the group on medication. This weight gain was lost during menstruation.

*Relationship of Crimes of Violence to the Phase in the Menstrual Cycle.*—This phase of the investigation was prompted by the known increase in irritability and tension during the premenstrual phase. Many reports in the literature indicate reactions of an antisocial nature at this time.<sup>6, 7, 8</sup> Novak<sup>7</sup> reported striking changes of personality during the premenstrual period, and

TABLE VI. OCCURRENCE RELATIVE TO MENSTRUAL CYCLE OF CRIMES OF VIOLENCE OF 58 PRISON INMATES

PHASE OF MENSTRUATION	NUMBER	PERCENTAGE
Premenstrual week	26	62
Midcycle	8	19
Menstruating	7	17
End of period	1	2
Total	42	100
No period	3	
Cannot remember	8	
No indication on records	2	
Pregnant	2	
Flowing from abortion	1	
Total	58	

Cooke<sup>8</sup> indicated that 84 per cent of all the crimes of violence in Paris, committed by women, are perpetrated during the premenstrual and early menstrual phases of the cycle.

In 58 instances investigated of imprisonment at Westfield for unpremeditated crimes of violence (murder, manslaughter, and assault), 62 per cent of the crimes were committed in the premenstrual week and 17 per cent during menstruation. Our findings are summarized in Table VI.

The relationship of hypoglycemia to electroencephalographic changes<sup>9</sup> and to criminology<sup>10</sup> has also been reported.

### Comment

The experiment was conducted under highly supervised and controlled environmental conditions. The relatively homogeneous character of a prison setting as compared to industrial or educational institutions was considered preferable for an experiment of this type.

The voluminous information obtained in individual interviews and observations of the inmates by the investigators as a check on the validity of the questionnaire method presented an impressive set of data. Since these data are not amenable to direct measurement by usual techniques, they were not reported in this paper in any detail. However, they indicate that the statistical result of analysis of the rating forms represents conservative findings of the effect of the medication and special diet. For instance, interviews with inmates who reported no improvement on the survey forms indicated that they were evaluating the medication on the basis of menstrual pain rather than on premenstrual tension and under more extensive but nondirective questioning many inmates indicated spontaneously some premenstrual tension reduction which they had not reported on the survey forms.

The symptomatic response to therapy could be classified into three groups: (a) nervous and mental symptoms, (b) symptoms due to fluid retention, and (c) menstrual disturbances. The greatest improvement was noted in the nervous and mental symptoms. This is aided by the synergistic effect of the protein of the milk and cheese in alleviating the hypoglycemic symptoms. The group consisting primarily of symptoms due to fluid retention showed slightly less marked improvement and the menstrual disturbances showed the least response.

### Summary

A study of 249 volunteers with premenstrual symptoms at Westfield State Farm indicated that 51 per cent of the prison population (131 of 257 inmates), with an average age of 32.4 years, and 33 per cent of the reformatory population (118 of 358 inmates), with an average age of 21.4 years, suffered from premenstrual tension.

Sugar tolerance tests showed a hypoglycemic-type curve in the premenstrual phase and premenstrual vaginal smears indicated hyperestrogenic stimulation.

Review of the inmates' records indicated that 62 per cent of crimes of violence were committed in the premenstrual week.

Therapy consisted of medication containing vitamin B complex and ammonium chloride, and supplementary feedings of milk and cheese in the premenstrual period. Analysis of the reported improvement indicates:

15 per cent of inmates reported improvement when given placebos only;

39 per cent of inmates reported improvement with placebos plus supplementary high-protein diet;

61 per cent of inmates reported improvement when given medication only;

79 per cent of inmates reported improvement when given medication plus supplementary high-protein diet.

Medication in this phase of the study is held to be effective on symptoms of premenstrual tension rather than on the underlying estrogen-progesterone imbalance.

Results showed increased work output, improvement in behavior and attitude, fewer requests for analgesic and sedative medication, less punishment for infraction of rules, and marked increase in the general morale.

The authors are indebted to Dr. Thomas H. McGavack for suggestions and constructive criticism; The Honorable Edward J. Donovan, Commissioner of New York State Department of Correction, and Dr. Herman E. Hilleboe, Commissioner of New York State Department of Health, and their respective staffs for cooperation and suggestions; Miss Ruth Collins, Superintendent, and Dr. Anna Nimelman, Resident Physician of the Women's House of Detention, New York City, for their aid in reviewing the original records of the inmates; and to Dr. George K. Higgins for the vaginal smear studies.

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660 MADISON AVENUE

## THE SYNDROME OF TESTICULAR FEMINIZATION IN MALE PSEUDOHERMAPHRODITES

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**T**HERE is a clinically recognizable syndrome found in patients who are essentially normal-appearing women, but who have undescended testes in place of ovaries.

The commonly accepted basis for the determination of the sex of an individual is the type of gonad present. These patients, therefore, are actually male pseudohermaphrodites, but the term "pseudohermaphroditism" usually connotes congenital abnormalities of the external genitals resulting in confusion of the sex. The individuals under discussion, however, are of typical feminine appearance with well-developed secondary sex characteristics and show normal female external genitals on clinical examination. Frequently the patients have been married with complete marital satisfaction, other than the complaint of sterility.

The clinician may be surprised when histologic section of the gonad reveals the patient's true status. Actually these patients present a fairly typical clinical picture. For this reason they have been singled out from the other forms of intersexuality, and we have called the clinical syndrome "testicular feminization."

The outstanding characteristics of this syndrome are:

1. Female habitus with normal female fat deposits. In some cases the build has a eunuchoid tendency with long extremities and large hands and feet.

2. Normal female breasts, often with a tendency to be "overdeveloped," although the nipples are sometimes juvenile.

3. Absent or scanty axillary and pubic hair in the majority of cases. There may be a slight amount of vulvar hair. The hair on the head is that of a normal female without temporal recession, but the facial hair is more often absent, as in a child.

4. Female external genitals. The labia may be underdeveloped, especially the labia minora. The clitoris is normal or small. The vagina ends blindly, but is usually adequate for marital relations.

5. Absence of internal genitals except for rudimentary uterine and other anlage, including sometimes Fallopian tubes or spermatic ducts, and for the gonads, which may be intra-abdominal or may lie along the course of the inguinal canal.

6. Gonads consisting largely of seminiferous tubules usually without spermatogenesis, but in most cases with a marked increase in interstitial cells. The picture is essentially that encountered in cases of undescended testes. Tubular adenomas are frequent findings. In a few cases there has been a considerable amount of fibrous stroma.

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7. Hormone assays in a limited number of cases suggest that these testes produce both estrogen and androgen. The pituitary gonadotropins have been elevated in some instances.

### Incidence

Although such a combination of findings might be thought to be extremely rare, review of the literature, a hazardous procedure, reveals a surprising number of cases that appear to fit into the criteria described. Attention has been called to this special form of pseudohermaphroditism by a number of authors, including Schiller<sup>72</sup> and more recently Wachstein and Scorza,<sup>81</sup> but its existence does not appear to be very widely recognized by clinicians. The cases encountered are listed in Table I.

All of the cases listed, unless otherwise noted, showed female habitus, fat deposits, and breast development. The hair on the head was female in all cases, and there was no facial hair or hirsutism. The external genitals were female, and the vagina, although varying in depth, was in most cases adequate for intercourse. When the gonads were in the inguinal canal, hernias were common. In a few cases the urethral orifice was patulous. The uterus and other internal genitals were rudimentary or absent. In all cases at least one gonad was histologically proved to be testis.

As in all such tabulations, it is difficult to know what to do about borderline cases or reports with insufficient data. Cases in infancy and prepubertal cases were excluded because the patients had no opportunity to complete the development of secondary sex characteristics. The only cases included without such development are those of Giusti,<sup>28</sup> Hain and Schofield,<sup>33</sup> and Bleyer<sup>10</sup> (Case 2); all of these patients were castrated before or during puberty.

There are also a considerable number of cases presenting the clinical findings of this syndrome in which no biopsy of the gonads was made. These cases are not included in Table I. The majority of patients in such cases, on the basis of their completely feminine appearance, were assumed quite naturally to have ovaries, but the statistical chance is greater that the gonads were actually testes.

It seems likely that this syndrome might be the correct diagnosis in a few cases reported as arrhenoblastoma (Behrend and Levine,<sup>6</sup> Dudman,<sup>24</sup> Javert and Finn,<sup>39</sup> Case 3). In these patients no ovarian tissue was demonstrated histologically and the uterus was reported as rudimentary or absent. Tubular adenomas and other tumors are frequent findings in the testicular feminization syndrome, sometimes completely replacing the gonad. Goldberg and Maxwell<sup>29</sup> originally thought their case was one of bilateral arrhenoblastomas with absence of the uterus, but subsequently in a very thorough report corrected this opinion.

There is a strong familial tendency as shown by the number of sisters with the same findings. The sterility of the patients prevents direct hereditary descent, but the history in Case 2 suggests five cases in three generations of the same family following the maternal line.

TABLE I

AUTHOR	DATE	AGE	FAMILY HISTORY	MARITAL HISTORY	HABITUS	HAIR		GONADS	COMMENTS
						AXILLA	PUBIS		
Steglehner	1817	23		Virgin	♀ appearance, hips, large breasts; ♂ voice, larynx		Scanty	Inguinal	Regular menstrual molimina; autopsy (♀ histologic methods)
Ricco	1832	80		Married	Well-developed breasts; ♂ voice, pelvis, and bones			Inguinal	Autopsy
Fioux	1871				♀ appearance and breasts			Labial	Paratesticular cyst present
Krabbel	1879	19		Libido 0	Heavy build, ♀ appearance; large breasts			Inguinal (removed); hydrocele on left	No menstrual molimina; died of peritonitis postoperatively
Chambers	1879-80	24		Libido 0	69" tall; ♀ voice, pelvis; large breasts; no nipples			Inguinal (removed)	Urethra admitted finger tip; left breast "disappeared" postoperatively
Jones	1890	21	2 sisters		Large stature; ♀ appearance, breasts; prominent larynx			Inguinal (removed)	No menstrual phenomena
Abel	1891	33		♀ libido	Small, ♀ appearance; small breasts, almost no nipples	0	0	R. inguinal L. pelvic sarcoma	"Regular menses" (♀ from urethral polyp); pelvic sarcoma; died postoperatively
Polaillon	1891	25		Prostitute	♀ appearance, voice, breasts; large hips			Inguinal	No molimina; autopsy showed coarctation of aorta
Blagowolin Kochenburger	1893 1893	28 33		M. 11 yr. M. 10 yr. Libido 0	♀ appearance, breasts Heavy; ♀ build; well-developed breasts		+	Labial (removed) Labial (removed)	No menstrual molimina Testicular adenoma present; urethra admitted finger tip
Braun	1894	28	0	Coitus + Libido 0	♀ face, build, breasts; ♂ pelvis, extremities, hands		Scanty	Inguinal (reduced; later removed)	Testicular tubular adenoma present in gonads
Martin	1894	20/21	Sister		♀ features and voice; breasts poorly developed		0	Inguinal (removed)	Hair growth, breast swelling, and hot flashes after castration
Will	1896	54		Coitus + Libido 0	Large heavy frame; ♀ breasts; rather deep voice		Scanty	Inguinal (removed)	Adenoma, cysts, sperm present; molimina, abd. pain q. 4 weeks; urethra admitted thumb tip

Clark	1898	42	M. 16 yr.	Well-developed breasts, rudimentary nipples; large hands	Scanty	Inguinal (removed)	Patient claimed regular menses
Kutz	1898	23	Single	♀ appearance; "virginal" breasts	+	R. ing.-labial (removed); L. ?	L. hernia with fibro-adenoma; abd., groin, breast pain q. 4 wk.
Schulze-Vellinghausen	1898	32		Medium-sized woman; ♀ pelvis, breasts; large bones, hands	Scanty	R. not felt L. inguinal (removed)	Paratesticular cyst; rudimentary uterus in hernia; abd. pain q. 3-4 wk.
Delagénère	1899	27		Tall, thin; prepubertal breasts; ♂ manner	Scanty	Inguinal (removed)	Adenomas of testes; occasional menstrual molimina (abd. pain); no hot flashes post-operatively
Matthews	1899	12/19		Tall, slim	0	R. not felt L. inguinal (removed)	Breasts not mentioned
Turner	1900	14		Well-developed breasts for age	Scanty	L. inguinal (removed)	"Caruncular" urethra
Demars	1903	41	M. 20 yr. Libido +	160 cm. tall; ♀ appearance, normal breast development	Scanty	Inguinal (removed)	Several small adenomas present
Helmbold	1903	28	Libido 0	165 cm. tall; ♀ features, build, pelvis; large breasts	0	Upper labial (removed)	Adenomas, adrenal-like nodule in gonad; paranoic; suicidal ideas
Hengge	1903	19	Sister Virgin ♀ libido	Big, heavy 178.5 cm. blonde; ♀ breasts, pelvis	0	R. labial (removed) L. inguinal (removed)	Cyst in l. epididymis; headache, nosebleeds, abd. pain q. 4 wk.
Schönfeld	1903	22	Single	♀ appearance, facies, and breasts	Scanty	R. inguinal (removed) L. abd.-ing. (removed)	Several paratesticular cysts
Marion	1905	36	M. 16 yr.	♀ appearance and breasts	+	R. inguinal L. abdominal tumor	Alveolar carcinoma replacing abdominal gonad
Amann	1906	29	0	♀ appearance, pelvis, breasts; long arms and hands	Sparse	Abdominal—near inguinal ring (removed)	Gonads described as "normal testes"
Blumreich	1906	22	Coitus + ♀ libido	♀ appearance and breasts		Inguinal (removed)	Severe postoperative psychosis
Gerbis	1907	22	Single ♀ libido	Heavy build; ♀ voice, facies, breasts; large hands	0	Inguinal (R. removed)	Tubular adenoma rt. testis; left breast larger than rt.

TABLE I—CONT'D

AUTHOR	DATE	AGE	FAMILY HISTORY	MARITAL HISTORY	HABITUS	HAIR		GONADS	COMMENTS
						AXILLA	PUBIS		
Loges	1907	33		Single Libido 0	♀ appearance, voice, hips, breasts		Scanty	Inguinal (R. re- moved, L. re- duced)	Testicular adenoma; nervous and irritable every 4 wk.
Heyn	1910	46	0	M. 21 yr. Libido +	Large 168 cm. woman; ♀ breasts, pelvis; long feet, hands	Scanty	Scanty	Inguinal (removed)	Paratesticular cysts; claimed irregular menses
Pozzi Case 2	1911	33	0	♀ libido	Medium height; ♀ pel- vis, voice, limbs; very large breasts		Scanty	R. inguinal (re- moved) L. labial (removed) Abdominal	Left paratesticular cyst; monthly molimina and nosebleeds
Bell	1916	23			♀ appearance; full breasts				
Wiener	1917	18			♀ appearance, well- developed breasts	0	0	Inguinal (R. re- moved; L. re- placed in abd.) R. abdominal L. inguinal (re- moved)	Small body like rudi- mentary uterus pal- pated in vault Adenomas; rudimentary uterus; simulated menses, miscarriages
Caturani	1917	26	Sister	M. 6 yr. Libido 0	♀ appearance, breasts, pelvis			R. labial L. inguinal (re- moved)	Numerous adenomas left gonad; rudi- mentary cervix, uterus
Schwartz	1919	25	0	M. 2 yr. Libido +	174 cm. tall; large feet; ♂ figure, bones; very big breasts	0	Scanty	R. abdominal (re- moved) L. abdominal (re- moved)	Ovary-like testicular stroma; seminoma re- placing left gonad
Skajaa	1919	25/30	Married		"Woman"			Rare interstitial cells; male character	
Bérard & Dunet	1921	23	Married No coitus		170 cm. tall; ♀ appear- ance, fat, breasts; ♂ legs, voice	Scanty	Scanty	L. abdominal tumor R. abdominal (re- moved)	Ovary-like testicular stroma; seminoma re- placing rt. gonad
Menetrier Case 1	1922	45	Sister Libido +		175 cm. tall; robust; ♀ face, well-developed breasts	+	+	L. abdominal (re- moved)	Adenomas; cysts of epididymis; no left gonad; no postopera- tive changes
Patzelt	1924	23	0	Coitus +	Heavily built; especially well-developed breasts	0	0	R. inguinal (re- moved) L. none	Came for fractured clav- icle; left femoral herniotomy at 9 yr.
Christopher	1924	9/17			Broad shoulders; very large breasts		Scanty	R. inguinal (re- duced) L. femoral (re- moved)	Cyst adjacent to rt. gonad; small adeno- ma; hot flashes post- operatively
Wagner	1927	13/21	Engaged Libido +		♀ appearance, voice, pelvis, well-developed breasts	Scanty	Scanty	Inguinal (removed)	



Antonopoulos	1929	38	M. twice Libido 0	64" tall; large bones; ♀ pelvis, larynx, breasts	0	Scanty	R. inguinal (re- moved) L. abdominal (re- moved)	2 small cysts adjacent to left gonad
Cotte & Pallot	1929	62	M. 32 yr. Libido +	♀ appearance and breasts			Inguinal (removed)	Ovary-like stroma; thought to be ovotestes
Schultze	1930	52	M. 33 yr. Libido +	163 cm. tall; long arms, hands, feet; ♀ voice; big breasts	0	0	Abdominal (re- moved)	Large cysts of both gonads
Odasso	1930	26	Single Libido 0	166 cm. tall; ♀ appear- ance, voice; well- developed breasts	0	+	R. inguinal (re- duced) L. inguinal (re- moved)	Eczema of face, head- ache, and breast pain q. 25-30 days
de Lima & Tavares	1930	48	Single Coitus +	♀ appearance; well- developed breasts	0	Scanty	Inguinal (R. re- moved)	Fibromyoxoma rt. labia; claimed rare menses
Orsós	1931	44	M. 24 yr. Libido +	♀ voice, breasts; broad shoulders			Inguinal (removed)	Small hydatid cyst on left; periodic nose- bleeds in youth
Pandolfino Case 1	1931	24	Sister Single Libido 0	♀ pelvis, voice, skele- ton, breasts			Inguinal (removed)	No menstrual molimina; 15 yr. old "sister," with inguinal gonads
Cadiz & Lipschütz	1933	22	Engaged Libido +	Well-developed breasts		+	Labial (removed)	Regular molimina with abd. pain; menopausal symptoms post- operatively
Creevy Case 1	1933	13		♀ breasts, skin, facies, contours			R. inguinal (re- duced); L. none	No left gonad
Case 2		17		♀ appearance and breasts			Inguinal (removed)	Nosebleeds once a month for 6 months
Carmichael & Oldfield	1934	14		♀ appearance; small rounded breasts; ♂ pelvis			R. abdominal (re- moved) L. abdominal tumor	Malignant teratoma re- placing left gonad; infantile uterus pres- ent
Assim	1935	22	0	180 cm. tall; long ex- tremities, large hands, feet; ♂ voice; well-developed breasts	0	Scanty	Inguinal (R. re- moved, L. placed in labia)	Regular molimina with headaches, abdominal and inguinal pain; large urethral orifice
Weyeneth Case 1	1936	25	0	♀ fat, voice; small pelvis; well-developed breasts	0	0	Inguinal (R. re- moved, L. re- placed in abd.)	Small cyst in epididy- mis; no postoperative changes
Krückmann	1937	25	Engaged	Short; ♀ appearance; large breasts	0	0	Abdominal	Numerous adenomas; monthly cramps; died after vaginal plastic

TABLE I—CONT'D

AUTHOR	DATE	AGE	FAMILY HISTORY	MARITAL HISTORY	HABITUS	HAIR		GONADS	COMMENTS
						AXILLA	PUBIS		
Mishell Case 1	1938	35	Aunt 2 sisters	Single	Height 67"; span 69"; ♀ appearance and breasts	0	Scanty	Inguinal (removed)	Estrogen up to 21 R.U./ 24 hr.; postoperative fall, hot flashes
Case 2		23		Single	Height 69"; ♀ appearance	0		Inguinal (removed)	Adenomas; estrogen up to 28 R.U./24 hr.; postoperative fall
Carlisle & Geiger	1938	20	0	M. 6 mo.	♀ appearance; well-de- veloped breasts; ♂ hands, pelvis	0	Scanty	R. inguinal (re- moved)	Androsterone 2.6 mg., estrogen 10 gamma/24 hr. postoperatively
Case 1 Palhares	1939	30	0	Single ♀ libido	Medium build; ♀ ap- pearance, well-devel- oped breasts		Scanty	L. abdominal Inguinal (removed)	Tubular adenomas pres- ent
Greenhill & Schmitz	1940	22	0	Single ♀ libido	71" tall; ♀ appearance, well-developed breasts		Scanty	R. abdominal L. inguinal (re- moved)	Adenomas; estrogen 4-8 R.U., gonado- tropin < 12 R.U. 10 mo. postoperatively
Weisman & Schwarz	1941	29	Sister	M. 8 yr. Libido 0	159 cm. tall; long ex- tremities; ♀ breasts, no nipples	0	0	Abdominal (R. re- moved)	Urinary estrogen, gonadotropin normal
Novak	1943	27	Sister	Married Libido +	♀ features, proportions, breasts	0	Scanty	Abdominal (re- moved)	Tubular adenomas; ovary-like stroma; hot flashes post- operatively
		26		Married Libido 0	55½" tall; short legs; breasts of 16 yr. old girl	0	Scanty	Abdominal (re- moved)	Adenomas almost re- placing gonads; rapid early growth, then ces- sation; hot flashes postoperatively
Baker Case 2	1943	17	Sister	M. twice	Well-developed breasts; ♂ leg hair		+	R. abdominal "ovary," L. inguinal (re- moved)	Rt. gonad not biopsied
Wenner & Scheidegger	1943	52		Coitus Libido +	Heavy build; ♀ pelvis; large pendulous breasts		0	Labio-inguinal (re- moved)	Tubular adenomas pres- ent; prolapse of va- gina
Jolles & Gleave	1945	51/61	0	M. 32 yr. Libido +	Medium build; ♀ ap- pearance and breasts		+	L. inguinal (re- moved)	Rt. malignant "arrhen- blastoma"; died with metastases
Case 1 Herweg	1946	15/18		♀ libido	64" tall; ♀ appearance; well-developed breasts	+	+	R. retroperitoneal Labio-inguinal (L. removed)	Negro; 17-KS 10 mg./ 24 hr.

Hain & ... 1947 2/14 69" tall; ♂ contour and ... 17-KS 11.9 and 6.7 mg./  
24 hr., estrogen < 2

Hain & Schofield	1947	2/14	69" tall; ♂ contour and pelvis; flat breasts	0	0	Inguinal (removed)	17-KS 11.9 and 6.7 mg./ 24 hr., estrogen < 2 I.U., pregnandiol 0, gonadotropin > 106 M.U.
Giusti	1948	7/18 } 7/16 }	156 cm. tall; ♀ voice, pelvis; breasts unde- veloped	0	0	Inguinal (removed)	Bilateral castration at 7 years; no breast de- velopment
			152 cm. tall; ♀ voice, pelvis; breasts unde- veloped	0	0	Inguinal (removed)	Bilateral castration at 7 years; no breast de- velopment
Goldberg & Maxwell	1948	19	Tall, eunuchoid; ♀ ap- pearance; large breasts	0	0	Abdominal (re- moved)	Adenomas; estrin effect in vaginal smear; FSH 96 M.U./24 hr.; 195 M.U.; hot flashes postoperatively
Bleyer	1948	19 } 12 }	♀ build, well-developed breasts	0	0	R. abdominal (re- moved) L. inguinal (re- moved)	Bilateral adenomas present
			♂ hairline and expres- sion			Inguinal (removed)	Prepubertal
Maggi	1949	18 } 16 }	♀ fat, face, voice; well- developed breasts; large hands	0	+	Labio-inguinal (re- moved)	Rare spermatozoa pres- ent; rudimentary uterus, cervix
			♀ appearance, pelvis; unusually large breasts; large hands	0	Scanty	Labial (removed)	Cremaster reflex pres- ent; adult bone cal- cification
Matheson	1950	8/19 } 3/17 }	66" tall; ♀ appearance, skeleton; well-devel- oped breasts	Scanty	Scanty	Inguinal (replaced in abdomen)	No visible clitoris
			70" tall; ♀ appearance; well-developed breasts	Scanty	Scanty	R. inguinal (re- moved) L. abdominal	
Soyer	1950	16	Pubertal ♀; breasts nor- mal for age	Scanty	Scanty	Inguinal (removed)	9 yr. old "sister" with inguinal testes
Ward-Mc- Quaid & Lennon Case 2	1950	20 }	♀ appearance with nor- mal breast develop- ment	Scanty	Scanty	Inguinal (replaced in abdomen)	No molimina; androgen 21 mg./24 hr.
Case 3		17 }	♀ appearance with nor- mal breast develop- ment	Scanty	Scanty	Inguinal (replaced in abdomen)	Androgen 8 mg./24 hr.
Wachstein & Scorza	1950	20	Slender girl, small ♀ breasts	0	0	Inguinal (L. re- moved)	Adenoma left testis; postoperatively 17-KS 8.7 mg., estrogen < 4 R.U., FSH > 80 M.U./ 24 hr.

The following two cases show the clinical picture of testicular feminization. The case from the Massachusetts General Hospital was that of a patient of Dr. J. V. Meigs, and the one from the Radiumhemmet in Stockholm is reported through the courtesy of Dr. H. L. Kottmeier.

### Case Reports

CASE 1.—D. P. (M.G.H. No. 563159). The patient was first seen at the age of 30 because she had never menstruated. The patient's general health was good. At the age of 13 the breasts had developed normally. They occasionally became sore, but this was not rhythmic. She had had no acne or cramps. Although unmarried, she had normal libido. She had a twin brother but there was no endocrine disorder in the family.

On physical examination the patient was tall with long arms and large hands and feet. Height was 181.5 cm., with a span of 187.4 cm. Blood pressure was 140/80. The voice was husky. The breasts were exceptionally well developed with a large areola around the nipples. There was no axillary and very scanty pubic hair. The clitoris was normal. The vagina appeared infantile and was about  $1\frac{1}{2}$  inches deep, ending in a blind pocket. There was no cervix or uterus palpable, but a mass could be felt in the left vault.

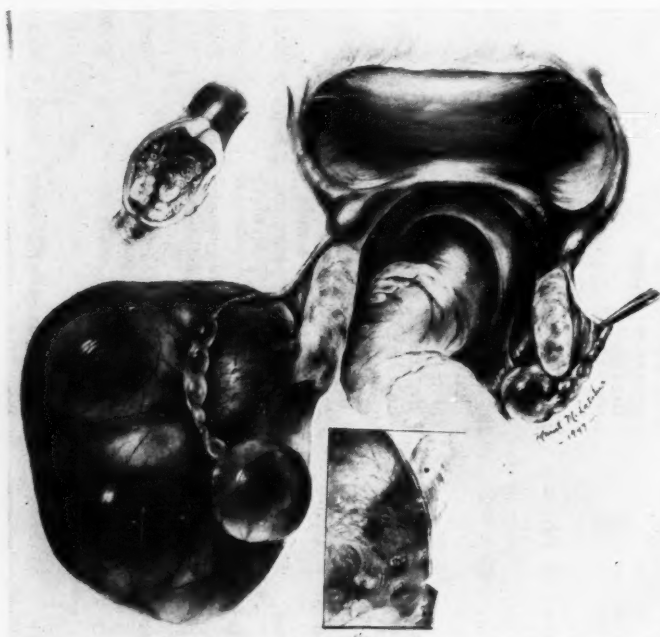


Fig. 1.—Operative view of the pelvis (Case 1), showing position of gonads and cysts. The symphysis is at the top of the illustration and the uterus is represented only by a band stretching between rectum and bladder.

Urinalysis was negative. Hemoglobin was 14.2 Gm. with normal white blood count and differential. Endocrine urinary excretion studies showed an increase in gonadotropins with an FSH positive for 96 m.u./24 hr. and negative for 192 m.u. The value for 17-ketosteroids was 13.4 mg./24 hr. and for estrin 32 R.U./24 hr.

Because of progressive increase in the size of the mass on the left, laparotomy was advised and performed at the age of 43. The mass proved to be a large cyst, arising from the left mesosalpinx. There was no uterus or cervix except for rudimentary uterine anlage which extended from the apex of the vagina up on either side toward the gonads, to which the cornua were attached. The gonads were about 2 cm. wide and 5 cm. in



length. There were small segmented tubes with cystic areas coming off the cornua of the undeveloped uterus. The operative findings are illustrated in Fig. 1. The appendix, the large cyst, the cystic tubes, and uterine anlage on the left were removed, and the right gonad biopsied.

The pathological specimen consisted of a 2 by 2 by 2 cm. "uterus" without cervix or endometrial cavity. There were two strings of thin-walled cysts, measuring up to 4 cm. in diameter, representing the "tubes," as well as one large thin-walled cyst measuring 15 by 8 by 8 cm. This large cyst contained some warty papillary growths at one end and was diagnosed as a papillary serous cyst. The left gonad was a sausage-shaped structure, measuring 5 by 2 by 2 cm., which on section appeared to be covered by smooth muscle. Its color was dark brown with oval nodules of firmer, light brown tissue, the largest of which was 1.2 cm. in diameter. The biopsy from the right gonad appeared similar in appearance.

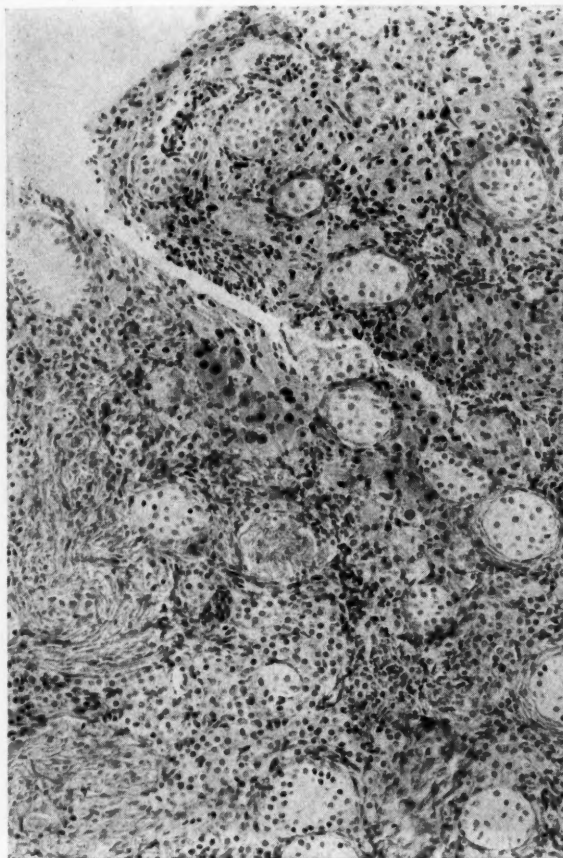


Fig. 2.

Fig. 2.—Section of gonad (Case 1). Rudimentary tubules and masses of interstitial cells predominate.

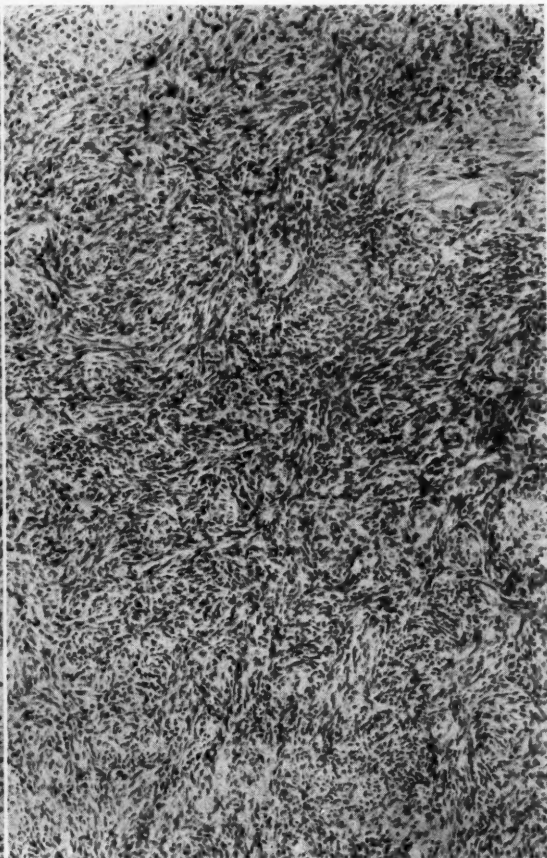


Fig. 3.

Fig. 3.—Section of gonad (Case 1). Area showing chiefly fibrous stroma. This resembles ovarian stroma, but no follicular derivatives are found.

Microscopically the gonads consisted of four elements irregularly intermingled, with each element predominating in certain fields: (1) Well-differentiated seminiferous tubules which were lined with Sertoli cells, but contained no spermatogenic cells (Fig. 2). (2) Leydig cells in large numbers, of varying size and degrees of differentiation which were imbedded in the stroma in some areas and in other areas grew in cords and small com-

compact nodules. These showed brightly acidophilic cytoplasm and a considerable proportion contained granules of bright brown pigment. (3) Stroma resembling cortical ovarian stroma but with a complete lack of follicles or any of their derivatives (Fig. 3). (4) Interlacing bundles of smooth muscle fibers, doubtless from the fusion of the gonad with the uterine anlage.

The patient had recurrent attacks of manic depressive psychosis and committed suicide at the age of 45. Section of the remaining gonad at autopsy showed the same structure as that of the surgically removed specimen. The adrenals were normal. A section of breast showed dense stroma in which were scattered ducts, but only one rudimentary lobule of glandular tissue.

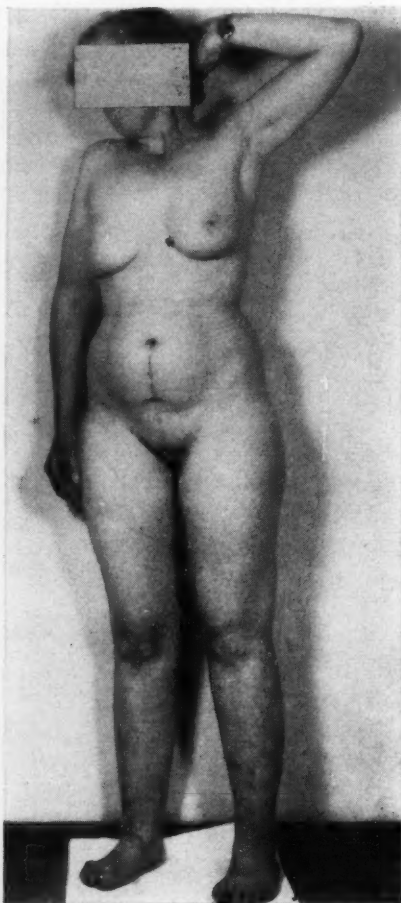


Fig. 4.—Case 2. Note female habitus, breast development, large hands, absent axillary and pubic hair.

CASE 2.—K. H. M. A. (Radiumhemmet Gyn. No. 252/1951). A 44-year old housewife was referred to the Radiumhemmet for radiological treatment following surgical removal of a dysgerminoma. Because of two episodes of colicky abdominal pain and fever, she had been admitted to an outside hospital, where she was found to have a tumor filling the pelvis and rising 2 to 3 fingerbreadths above the symphysis pubis. Among other observations, the vagina was described as being of normal depth, but no uterus or cervix could be felt. An operation was performed, revealing a grapefruit-sized tumor on the left side of the true pelvis. This had the gross appearance of a fibroid, although no uterus or ovaries could be found. There was only a fold in the pouch of Douglas and what appeared to be a

round ligament on each side. During the removal of the tumor it was noted that part of the blood supply seemed to come from the ovarian artery. The tumor weighed 800 grams. It was described as resembling a myoma which was edematous and somewhat necrotic in the center. Over part of the tumor was a capsule, which contained what was thought to be another flattened myoma. Of the specimen only a small part was sent to the pathologist. The microscopic diagnosis was dysgerminoma.

The patient's history revealed that she had developed normally but had never menstruated or had menstrual molimina. For this she had consulted a doctor on two occasions and was told that there was nothing to do about it. She had been married for 20 years with normal coitus, libido, and orgasm, but had had no pregnancies. The patient was an only child. Her mother had three sisters who had never menstruated, two of them married, one still living and well at 97 years of age, and her maternal grandmother had one sister who had never menstruated.

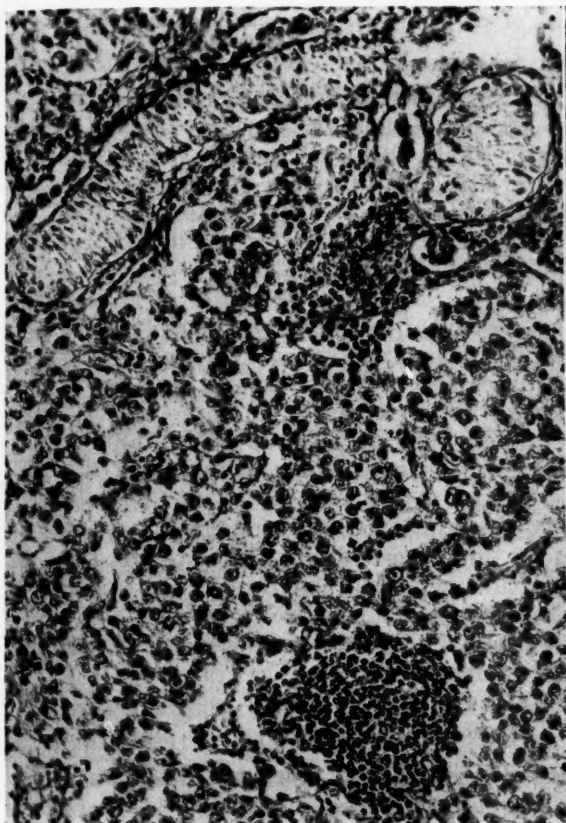


Fig. 5.

Fig. 5.—Section of seminoma (or dysgerminoma) in Case 2, with tubular structure present.

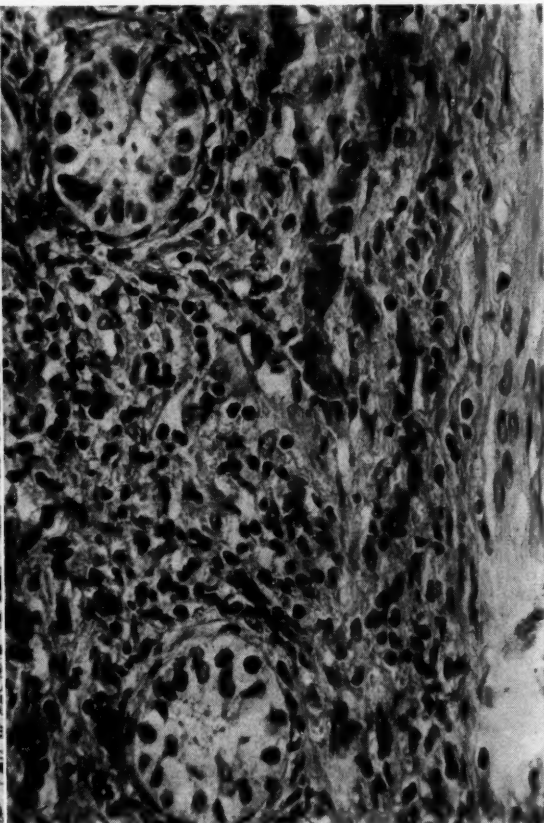


Fig. 6.

Fig. 6.—Higher magnification of tubules (Case 2). Note similarity to tubules in Case 1.

When seen at the Radiumhemmet, physical examination showed a patient with typically feminine habitus and a well-healed midline operative incision (Fig. 4). Height was 173 cm., span 180 cm., and weight 80 kilograms. The hands were rather large; breasts were well developed. There was no vestige of hair on the face, and no axillary or pubic hair other than a trace of down on the vulva. The clitoris and labia minora were underdeveloped. The urethral orifice was patulous and showed some mucosal prolapse. The vagina ended in a blind pouch 8 to 10 cm. in depth, and no organs or masses could be felt



in the pelvis or in either inguinal region. Hemoglobin was 82 per cent, red blood count 4.5 million, white blood count 4,300. X-ray films were interpreted as showing an essentially normal female pelvis. Chest film revealed no metastases. Vaginal smear taken six months after operation showed predominantly precornified cells, but occasional cornified superficial cells with some estrogen effect. In a smear taken four months later this slight estrogen effect had disappeared. Hormone assays eight months postoperatively showed that the urinary estrogen was less than 20 m.u./liter, and the 17-ketosteroid excretion was 4.8 mg./24 hr. The FSH was 96 m.u./24 hr. The patient had had no hot flashes since operation.

Unfortunately only one block of the original tumor was available for study. Review of the available pathological slides revealed the presence of tubules of a testicular type scattered through the tumor, which otherwise showed the typical picture of a dysgerminoma or seminoma (Figs. 5 and 6). There were no Leydig cells to be seen. It is a matter of speculation what the small flattened "myoma" on the surface of the tumor was. This may possibly have been the remainder of the gonad, or even the opposite gonad, as a unilateral gonad is very uncommon.

While it must be acknowledged that a dysgerminoma may contain a variety of structures, the clinical picture was so clearly that of the testicular feminization syndrome, that it seems quite likely that this patient never had an ovary. The tubules were not characteristic of any of the structures seen in a normal ovary, and appear completely similar to the tubules described in the first case above. The well-known tendency for tumors to develop in undescended testes makes it not improbable that this was actually a case of a seminoma developing in such a gonad.

Similar cases have been reported by Neugebauer<sup>58</sup> and by Marip<sup>52</sup> where it has been impossible definitely to establish the sex because of neoplasm replacing a single gonad. In both these cases the clinical picture appears to have been that of the testicular feminization syndrome. In one case no ovarian or testicular tissue could be found in a carcinomatous gonad, and in the other the solitary gonad had been replaced by sarcoma, although a vas deferens led into the tumor.

Skajaa<sup>77</sup> and Menetrier and his co-workers<sup>56</sup> reported married women with an abdominal testis on one side and a tumor resembling seminoma on the other. The presence of occasional immature seminiferous tubules scattered through the tumor in Menetrier's<sup>56</sup> case presents a picture very similar to Case 2. He described a transition from tubular elements to neoplastic tissue, which were also noted in some areas in our tumor.

### Hermaphroditism and Differential Diagnosis

True hermaphrodites, sometimes called "glandular" hermaphrodites, are individuals who possess both ovarian and testicular tissue, either as separate gonads, or combined as an ovotestis. There are at present more than forty histologically proved cases of this type reported in the literature. The associated abnormalities of the genital tract have been varied and bizarre, but have never been such as to permit self-fertilization, although in some cases there has been some evidence of both ovum and sperm production.

Pseudohermaphrodites, also known as "tubular" hermaphrodites, possess the gonads of one sex only but have some of the reproductive organs of the opposite sex. They are classed as male ("androgynoid") or female ("gynandroid") on the basis of whether the gonads are testes or ovaries. At times the term has been rather loosely applied to any individual in whom confusion of the sex has resulted from congenital abnormalities of the genitals, such



as varying degrees of hypospadias or enlargement of the clitoris. For details of the genital abnormalities, which may take innumerable forms, one should consult the monumental collection of cases by Neugebauer,<sup>58</sup> or the more recent work by Young.<sup>91</sup>

The existence of the true hermaphrodite with ovotestes, or both ovary and testis, while a rarity, proves that the X-X and X-Y chromosome relationship is not an "all or none" phenomenon, and that true masculinity and femininity can exist in the same individual.

Goldschmidt<sup>30</sup> was able to produce various degrees of intersexuality in butterflies. He came to the conclusion that there could exist different valencies of the sex chromosome which, if greater or less than normal, might result in intersexes. He further postulated that in such cases development starts according to one sex, and that then a specific turning point is reached from which development continues according to the opposite sex. Any differentiation which has been already reached, however, is maintained, including the gonads. Thus if the turning point occurs late in development, a gonad having the morphological make-up of a testis may function as an ovary and produce female sex hormone.

Much experimental work has also been done in producing sex reversal in animals, and on the effect of hormones administered during gestation in producing intersexual changes.

Whatever the theoretical background, the abnormalities in the vast majority of human intersexes are such that there is little likelihood that they be confused with the special type presenting the characteristics of the syndrome under discussion, in which normal female external genitals are present without enlargement of the clitoris. Not all pseudohermaphrodites with undescended testes and somewhat female-appearing external genitals will show feminization and the other findings of this syndrome (Novak,<sup>60</sup> Neugebauer<sup>58</sup>), but in all such cases the clitoris is reported as enlarged or peniform. No case was encountered with a normal vulva and normal clitoris in which there was not feminization, unless the testes had been removed prior to full maturity.

There are a considerable number of cases of male pseudohermaphrodites with malformed external genitals who have breast development and female configuration (Young,<sup>91</sup> Neugebauer,<sup>58</sup> Witschi and Mengert<sup>90</sup>). Such patients usually have normal pubic hair development. In cases with deformity of the external genitals, the breast development and secondary sex characteristics seem to be unpredictable and may be either male or female.

There appears to be no exact counterpart of this syndrome in the "opposite sex," i.e., normal male external genitals and secondary sex characteristics with ovaries in place of testes. There are, however, cases reported with male habitus and an almost normal penis in which the gonads proved to be ovaries (Neugebauer<sup>58</sup>). The gonads were undescended and the scrotum absent. This demonstrates that the ovaries may have androgenic capacities.

It may be a problem to differentiate between cases with the testicular feminization syndrome and patients with uterine agenesis alone. In the latter instance the hair distribution should be more nearly normal female, and one

would expect normal gonadotropin excretion. Werth,<sup>86</sup> Peuch,<sup>67</sup> Nicaise,<sup>59</sup> Englisch,<sup>25</sup> and others have reported ovarian hernia associated with rudimentary development of the Müllerian system, which might present even more of a problem of diagnosis. In Werth's<sup>86</sup> case there was scanty pubic hair, but the breasts were flat and there was associated bilateral descent of the kidneys. In any case of uterine agenesis, one should at least suspect the possibility of testicular feminization.

In a few cases of women with inguinal gonads and an absent or rudimentary uterus, the pathologist was unwilling to commit himself as to whether the gonad was an ovary or a testis (Häberlin,<sup>32</sup> McMillan<sup>49</sup>). In one such case Reinberger and Simpkins<sup>70</sup> describe, in addition to testicular areas in the gonad, areas with degenerating follicles and "genitaloid cells" of the early fetal ovary. If this is a true ovotestis, it may be that there are stages between the gonads of the testicular feminization syndrome and those of the true hermaphrodite.

### Endocrine Aspects

One of the most interesting aspects of abnormalities of this sort is the unusual opportunity afforded to study the endocrine functions of the gonads.

The few estrogen and androgen, or 17-ketosteroid, excretion studies that have been done show values within the normal variations of both male and female. As these values overlap in the two sexes, they do not aid in establishing the sex.

Androgens are excreted by these patients, but it must be remembered that during active reproductive life women excrete almost as much androgen as men. The 17-ketosteroid excretion, reflecting both adrenal and testicular hormone production, was 13.4 mg./24 hr. in Case 1. This is in the middle of the range of values found in the men and among the upper normal values found in women. Herweg and his associates<sup>37</sup> and Hain and Schofield<sup>33</sup> found preoperative 17-ketosteroid values of 6.7 to 11.9 mg./24 hr. and normal androgen excretion has been reported by Ward-McQuaid and Lennon<sup>83</sup> in cases of this type.

The androgens, in any case, are insufficient to produce virilizing symptoms. The larynx has sometimes been reported as large with a husky voice, and the patients may be tall with broad shoulders, but there is no vestige of hirsutism or evidence of enlargement of the clitoris.

The completely feminine characteristics of these patients suggest the presence of some estrogen-like hormone. The amount of estrogen excreted in the urine in Case 1 (32 R.U./24 hr.) is within the normal range of women. Mishell<sup>57</sup> reported values up to 28 R.U./24 hr. in similar cases.

However, this estrogen-like hormone exhibits some differences from normal estrogen. For example, some of the secondary sex manifestations do not show the complete normal response to estrogen. Thus, although the breasts are large, in a number of cases the nipples or areolae are described as poorly developed. Also in two cases in which sections of the breast were made (Case 1 and that of Krüekmann<sup>44</sup>) the stroma was well developed, but there was

very little glandular tissue found. The vulva also shows a lack of estrogen effect with underdevelopment of the labia, especially the labia minora, and absence of pubic hair, giving it a prepubertal appearance. The impression is left that although the breasts are unusually large, in some other respects the patients grow up without completing puberty.

The estrogen is not sufficient to inhibit the pituitary gonadotropins to the same degree as normal estrogen, as reflected by the somewhat elevated FSH values. Hamblen and his associates<sup>34</sup> have noted hypergonadotropinuria in a group of male pseudohermaphrodites. They attributed this to a degeneration of the seminiferous tubules and the consequent failure of the release of a pituitary-inhibiting, estrogen-like hormone by these tubules. In Case 1, however, the FSH of 96 m.u./24 hr. was moderately elevated in the presence of normal estrogen excretion. Goldberg and Maxwell<sup>29</sup> reported an identical value in the presence of a vaginal smear showing estrogen effect. This suggests that there may be a qualitative rather than quantitative difference in the hormone.

The view may be held that hormones produced by the adrenals are responsible for the estrogenic effects produced. The evidence afforded by castration, however, points toward the testes as the source of this estrogen-like hormone. Mishell noted normal preoperative estrogen but found almost complete disappearance of the estrogen in two cases several months after castration. Studies in Case 2 above showed insignificant amounts of estrogen post-operatively. Goldberg and Maxwell<sup>29</sup> noted a rise in gonadotropins, loss of estrin effect in the vaginal smear, hot flashes, and some breast atrophy following castration, also suggesting a testicular source of the estrogen-like effect.

Information on the role of the gonads in producing secondary sex characteristics in these cases is afforded by two cases reported by Giusti:

Two sisters with normal genitals, absent uteri, and inguinal testes had bilateral castration at the age of 7 years. When seen subsequently at the ages of 18 and 16, they were, respectively, 156 cm. and 152 cm. tall. Their behavior and appearance were female, except that there was no breast development. A few small glands could be felt in the older girl. The pelvis and hips were female. There was no axillary or pubic hair other than fuzz on the mons, and the labia minora were underdeveloped.

Thus it appears that the hormones produced by the testes in these cases have little influence on factors such as the shape of the pelvis, but have an important effect on the production of breast development and perhaps some relation to growth.

Androgen and estrogen both play a role in growth. Androgen augments growth, but is not always a necessary factor, as male hypogonads reach normal height. The action of the sex hormones is believed to close the epiphyses. As has been previously mentioned, some cases of testicular feminization tend to show a slightly eunuchoid build with long extremities. This increased growth of the long bones could reflect a failure of epiphyseal closure, perhaps due to lack of inhibition of the pituitary growth hormone by the sex hormones. The short stature in the castrated cases of Giusti<sup>28</sup> suggests, however, that the presence of some amount of sex hormones may be a stimulus to growth.

Another possibility is that some somatic factor in the bones themselves may play a role. The breasts, the bony pelvis, the long bones, and other struc-



tures may be somatically "male" or "female," requiring relatively small amounts of the proper sex hormone for their development. On the other hand, if the end organ is of the opposite sex, relatively large amounts of hormone may produce only a limited response. No amount of androgen will make a penis out of a clitoris. The administration of estrogen to a male may produce gynecomastia, but it does not ordinarily produce the jumbo-sized breasts seen in some of these patients.

Similarly, the failure of hair development may be a somatic defect with absence of hair follicles, although in both of the reported cases above fine vulvar hair was present. The absent or scanty axillary and pubic hair is a significant finding from the point of view of clinical diagnosis, but it is hard to explain from the endocrine point of view. Occasionally the growth of pubic and axillary hair is normal, as in a 15-year-old Negro girl reported by Herweg and his associates. Kochenburger<sup>42</sup> and Marion<sup>51</sup> report cases with pubic hair, but the axillary hair is not mentioned. Kutz describes a case with abundant axillary but sparse pubic and anal hair. In Goldberg and Maxwell's case, the administration of estrogen following castration failed to cause hair growth. How much of the secondary sex manifestations are due to hormones alone, and how much to the end organ's ability to respond to hormone stimulation is difficult to determine.

### Pathologic Findings

The histopathology of the gonad is essentially that of the cryptorchid testis. The seminiferous tubules are immature, and sometimes hyalinized. Occasionally incomplete spermatogenesis is found but more often Sertoli cells predominate, and there may be no lumen present. The interstitial cells usually show a marked increase in spite of the lack of virilizing effect clinically.

Varying amounts of fibrous stroma are sometimes found to be present. Because of resemblance to ovarian stroma, J. Novak<sup>61</sup> considered his two cases as ovotestes with tubular adenomas, and our Case 1, in which the stroma was quite pronounced, was also originally thought to be a case of ovotestis. Also in the cases of Cotte and Pallot<sup>20</sup> and Menetrier and associates<sup>56</sup> it was suggested that the gonads might be ovotestis because of the ovary-like stroma. As this stroma is rather nonspecific, it seems wiser to reserve the term ovotestis for cases with more definite ovarian elements, such as follicles or their derivatives present.

It may be argued that this stroma plays a role in the estrogen production seen. In Case 1 fat stains showed it contained relatively little lipoid, which was concentrated in the tubules and to a lesser extent in the Leydig cells. Also in most of the cases described with a pronounced feminization, there was little or no stroma found.

Testicular tubular adenomas were a usual finding and were frequently multiple. Malignant sarcomatous or carcinomatous change occurred in the cases of Abel,<sup>1</sup> Marion,<sup>51</sup> Jolles and Gleave,<sup>40</sup> and Carmichael and Oldfield.<sup>15</sup> Seminomas were found in the cases of Menetrier and his associates,<sup>56</sup> Skajaa,<sup>77</sup> and in Case 2. In the last-mentioned case and those of Neugebauer<sup>58</sup> and Marip<sup>52</sup> it had destroyed the gonad so as to make the diagnosis of the patient's sex open to question.



Frequently cysts were reported in the epididymis or paratesticular structures, although they rarely reached the size of the one in Case 1. Rudimentary cordlike structures representing the vas deferens or the Fallopian tubes were noted. The musculature of the uterine anlage was sometimes fused with the gonad. The uterus was usually absent or represented only by a band of smooth muscle stretching across the pelvis. The only case in which a recognizable cervix and uterus were present was that of Carmichael and Oldfield.<sup>15</sup> (Although this was an undeveloped infantile structure, perhaps this patient should not be included in the series.)

### Psychosexual

From the psychosexual aspect these patients are definitely female. As in all intersexes, there seems to be an unusually high incidence of psychosis and suicide, especially when the patient has commenced to suspect she is abnormal, sometimes as the result of overzealous medical attention.

The patient herself first suspects this abnormality when she fails to menstruate. The adjustment to this alone is difficult, and in a considerable number of cases the patient has claimed regular menstrual menses and abdominal cramps (Krückmann,<sup>44</sup> Steglehner,<sup>79</sup> Kutz,<sup>45</sup> Delagénère,<sup>22</sup> Hengge,<sup>36</sup> Cadiz and Lipschütz,<sup>15</sup> Assim,<sup>4</sup> and Schulze-Vellinghausen<sup>75</sup>), vicarious nosebleeds (Pozzi,<sup>69</sup> Hengge<sup>36</sup>), or even menses themselves (Clark,<sup>19</sup> Heyn,<sup>38</sup> Abel<sup>1</sup>), even when manifestly impossible.

The sex urges of the patient are usually the same as those of other women, an indication that the seat of libido is more in the psyche than the gonads. The urge for childbearing is strong and some of the married patients have sought medical advice for sterility. It goes without saying that it would be unwise to inform the patient of the true state of affairs. To go one step further, in view of the long and happy marriages some of these patients have had, it seems unfortunate that in some cases the doctor has felt it necessary to tell the patient she must never marry. It seems only necessary to state that childbearing is impossible. Whatever the legal, moral, or religious view of this unusual circumstance may be, where male is married to a female with male gonads, the obvious humane attitude is not to interfere and by such meddling produce a psychiatric casualty and perhaps a suicide.

### Treatment

Owing to the role of these gonads in producing female development, it would seem justifiable to leave them in place until such development has occurred. If seen during puberty it might be worth while providing supplementary estrogen to see if more complete feminization could be obtained such as development of the vulva and production of pubic hair, and to see if the stature and build could be made more typically female by earlier epiphyseal closure.

After adolescence surgical removal then appears advisable to avoid the very real danger of neoplasia. In addition to adenomas and cysts there were seven malignant tumors out of the eighty-two cases collected. Castration has

resulted in hot flashes, rise in gonadotropins, diminished estrogen excretion, loss of estrogen effect in the vaginal smear, and atrophy of the breasts, and therefore estrogen substitution therapy may have to be instituted.

### Summary

There is a clinically recognizable syndrome found in patients who are essentially normal-appearing women, but who have undescended testes in place of ovaries. The most significant features are:

1. Female habitus, breast development, and other secondary sex characteristics.
2. Scanty or absent axillary or pubic hair in most cases.
3. Female external genitals, with a tendency to underdevelopment of labia, and a blind-ending vagina.
4. Absence of internal genitals except for rudimentary anlage and for gonads which may be located intra-abdominally or along the course of the inguinal canal.
5. Gonads histologically consistent with undescended testes.
6. Urinary excretion studies have suggested such testes produce estrogen and androgen. Elevated urinary gonadotropins have also been found.

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## CARCINOSARCOMA OF THE ENDOMETRIUM

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IT IS paradoxical and perhaps inevitable that, in many instances, as the volume of medical literature increases, so does the confusion regarding certain clinical entities. Such is the case in respect to the subject of carcinosarcoma of the endometrium, where considerable controversy now exists as to whether this is a distinct entity, or merely a variation of the universally recognized adenocarcinoma.

A variety of combined or associated neoplasms has been labeled "carcinosarcoma," dependent to a great extent upon the interpretation of the individual observer. Apparently, early observers were unaware of the ability of neoplastic cells to assume bizarre and atypical forms with a resultant sarcomatous appearance. Ewing<sup>1</sup> states that there is little doubt that many so-called carcinosarcomas result from the atypical growth of epithelial cells. The metastases are usually carcinomatous. He added further that the exudation and inflammation accompanying tumors of the endometrium greatly favor atypical cell growth.

Willis<sup>2</sup> states that osseous or cartilaginous metaplasia in the fibroblastic stroma of uterine carcinomas is not very uncommon and that this possibility must be taken into account in interpreting the structure of some supposedly mixed tumors of the uterus. In 1924, Nicholson<sup>3</sup> depicted the formation of nodules of hyaline cartilage in the stroma of an adenocarcinoma of the endometrium.

In view of these pathological facts, the reports of carcinosarcoma of the uterus by some early observers should be discarded and the neoplasm classified as pure carcinoma with extensive spindle-cell metaplasia.

Saphir and Vass<sup>7</sup> reviewed thirty-six such cases. In nineteen instances, pedunculated tumors projected either from the endometrium into the uterine cavity, or from the cervix into the vagina. Microscopically these consisted of large spindle-shaped or elongated cells similar to smooth-muscle cells among which many atypical anaplastic cells of varying sizes and multinucleated giant cells were also seen. Ulceration of the surface of the tumor was present in most instances and inflammatory changes were regularly evident within the stroma. The tissue of the base of the pedunculated mass was purely carcinomatous. Upon re-evaluation, Saphir and Vass considered these tumors as primary carcinomas invading myofibromas. In eight other instances, parts of the tumors were distinctly carcinomatous. In other regions, chronic productive inflammatory changes were present which were responsible for the pleomorphism of the tumor cells. These authors concluded that in the thirty-six



instances of so-called carcinosarcoma of the uterus, it was apparent that not only was sufficient evidence for such a diagnosis lacking, but that the potentialities of neoplastic tissue could account for the increased anaplasia leading to the dual diagnosis of these tumors.

Harvey and Hamilton<sup>8</sup> maintained that there is a double tumor which is a mixture of carcinoma and sarcoma and that this may be called carcinosarcoma. However, since they were of the opinion that the sarcomatous development was probably an exaggeration of stroma reaction to invasion by carcinoma, the picture could not be considered as one of a separate entity.

Hoffman<sup>9</sup> classified as carcinosarcoma a case of myosarcoma of the myometrium with an overlying papillary adenocarcinoma of the endometrium. It is obvious that these tumors arose from two separate tissues of the uterus, and, therefore, could not be classified as a single tumor of the endometrium.

Willis has summed up the argument against the existence of a carcinosarcoma of the endometrium by stating that the term implies either: (a) simultaneous malignant neoplasia in two distinct tissues, an epithelial tissue and its nonepithelial structure; or (b) consequent sarcomatous change in the stroma of a carcinoma.

With the exception of sarcomatous changes in the previously benign connective tissue in a mammary fibroadenoma, he knows of no reported instance in tumor pathology in which the interpretation of sarcomatous change in the stroma of an epithelial tumor is beyond doubt. Willis<sup>3</sup> also emphasizes the dictum that anaplastic tumors, especially carcinomas, often display misleading microscopical appearances simulating those of other kinds of tumors, and adds that diffusely growing carcinomas have often been diagnosed as sarcomas. According to this author, the diagnosis of "carcinosarcoma" has been particularly fallible and the great majority of tumors so designated have been pleomorphic carcinomas.

It would appear from the foregoing, therefore, that there is no justification in classifying certain tumors as carcinosarcomas of the endometrium. Under these conditions might it not be advisable to accept the recommendations of the aforementioned authors to reconsider these cases as pleomorphic adenocarcinomas of the endometrium? Before we can answer this question with any degree of confidence, it is necessary to consider the evidence which has led competent observers to maintain that a distinctly separate entity exists. There must be some differences in histologic appearance from that of the usual carcinoma of the endometrium upon which these authors base their conclusions.

Meyer, who is quoted by all authors, classified the tumors under discussion in three groups according to possible modes of origin:

1. *Collision tumors*: two primarily independent tumors each invading the other.
2. *Combination tumors*: the product of the growth of two different blastomatous portions derived from one stem cell.

3. *Composition tumors*: in which both parenchyma and stroma have become carcinomatous.

In discussing a recent paper by Hardy and Moragues on the subject of mesodermal mixed tumors of the body of the uterus, Novak<sup>10</sup> stated that at times mesodermal tumors contain epithelial elements because the mesoderm of the genital apparatus is capable of differentiating into either connective tissue or epithelium. Furthermore, the epithelial elements in the tumor may appear in the form of adenocarcinomas. According to Novak, such a combination of carcinoma and sarcoma represents a carcinosarcoma in the strictest sense of the term and the only one accepted by many pathologists. The mere existence of carcinoma and sarcoma in the same uterus does not constitute a carcinosarcoma, but rather a "collision" tumor as defined by Meyer. Novak's experience has been that in most cases which have been designated as carcinosarcoma, the supposed sarcoma represents only an extensive infiltration of the stromal cells which change their morphology and resemble sarcoma cells. He stated further, that, according to strict histologic definition, only the "composition" tumors (in which both carcinomatous and sarcomatous elements arise from the same stem cells) are entitled to the designation of carcinosarcoma. This limitation makes them very rare. Novak cautions against the too loose application of the term carcinosarcoma.

To add further to the confusion regarding the subject under discussion, Dixon and Dockerty<sup>11</sup> in 1940 employed the term "carcinosarcomatodes" to designate a single neoplasm having the morphologic features of carcinoma and sarcoma. They described the case of a 44-year-old white nullipara in whom a diagnostic curettage revealed the presence of a fibrosarcoma. A radical hysterectomy was performed, at which time multiple leiomyomas were observed. On the endometrial surface immediately above the internal os of the cervix, there was a 5 mm. sessile polyp, which, on microscopic examination, presented a combination of sarcoma and carcinoma, mostly carcinoma. In certain parts of the polyp, there appeared to be a line of demarcation between the sarcoma and the carcinoma. In other parts, the appearance was that of isolated carcinomatous glands dipping down into a sarcomatous stroma.

Lisa, Hartmann, Bayer, and Bonar<sup>12</sup> reported a case of carcinoma of the endometrium with the stroma consisting of atypical cells showing marked variability in size, hyperchromatism of the nuclei, and atypical mitoses. Eighteen months following hysterectomy, the patient died from retroperitoneal metastatic sarcoma. On this basis, the authors reclassified this as a case of carcinosarcoma. They reported a second case which occurred ten years following the induction of menopause with radium.

Raferty<sup>13</sup> observed a 62-year-old white woman in whom the diagnosis of carcinoma of the endometrium had been made following a diagnostic curettage. Six weeks following the intracavitary application of radium for 5,000 mg. hr., a total hysterectomy had been performed. The uterus showed a necrotic, boggy, papillary mass 3.0 by 2.5 by 2.5 cm. attached to the endometrium in the center of the uterine wall by a pedicle 1.2 cm. in diameter. Sections from this mass and from the adjacent uterine wall showed a few nests of degenerative

stroma. Seven months later, the patient was readmitted to the hospital with a metastatic vaginal mass which was found to be anaplastic sarcoma. As a result of this finding, the stroma reaction noted in the original reports was interpreted as sarcoma, and the diagnosis changed to carcinosarcoma.

Goodfriend and Lapan<sup>14</sup> removed a 7 by 7 by 3 cm. uterus from a 60-year-old patient. The endometrial cavity contained a large, irregular, polypoid tumor with areas of necrosis on the surface. Microscopic examination of the tumor disclosed the tissue to be composed of large masses of sarcoma, spindle-cell type, with some areas showing unusual atypism of the nuclei. In addition, there were large zones of adenocarcinoma and portions showing comingling of both tumors. Sections from one side of the tumor consisted of adenocarcinoma. Those from the opposite side consisted of sarcoma, and those taken from the central portions were mixtures of both. This evidence strongly suggests a "collision" tumor.

Lisa, Pack, and Gioia<sup>15</sup> reported the case of a 64-year-old Filipino who had a diagnostic curettage for vaginal bleeding of three weeks' duration. The curettings were diagnosed as endometrial adenocarcinoma. A radical panhysterectomy followed. The pathology was reported as primary endometrial carcinosarcoma, fibromyoma of the uterus, and primary squamous-cell carcinoma of the cervix. The authors stated that carcinosarcoma of the endometrium is almost invariably polypoid, and, in the majority of cases, originates from the midline of the fundus or the posterior wall of the uterus. The tumor is usually soft, grayish pink, and sessile. The surface may be ulcerated or intact. They stated further that in reviewing other case reports, it was observed that none of the metastases exhibited the combined mixed tumor, that is, the metastases were either carcinomatous or sarcomatous. Were they to contain a mixture of both types of cells, the identity of the primary neoplasm would be assured. However, since this phenomenon seldom occurs, Lisa and associates assume that the composite elements of the tumor are capable of behaving in a dissimilar manner.

Hill and Miller<sup>16</sup> apply the term "carcinosarcoma" only to those neoplasms with intermixed carcinomatous and sarcomatous elements. They concur in the opinion that the final proof of the existence of this entity lies in the presence of both elements in the metastases, a criterion which is seldom fulfilled. Two of the four cases reported by them, in addition to the case discussed by Goodfriend and Lapan, met this specification.

Confronted with the beforementioned conflicting opinions relative to the status of carcinosarcoma of the endometrium, I reviewed the records of the Tumor Clinic of the Hartford Hospital. Investigation disclosed that from 1939 through October, 1952, eight cases, including one treated by me (Case 8), had been classified as carcinosarcoma. A résumé of the clinical course and pathological findings in each case follows.

### Case Reports

CASE 1.—Mrs. M. R. (No. 366-656), a 72-year-old white para iii, gravida iii, was admitted to the Hartford Hospital on Feb. 28, 1939. She had been admitted to a hospital in a neighboring city on Jan. 27, 1939, with a chief complaint of a brownish vaginal discharge

which had been noted for five months, and a sudden uterine hemorrhage which had occurred on the day prior to admission. Normal menstruation had terminated thirty-five years previously. Carcinoma of the endometrium was diagnosed from curettings obtained on the day of admission. Transfer to Hartford Hospital for radiation therapy was recommended.

Another curettage was performed at this hospital and radon was inserted into the uterine cavity for a total of 3,300 mc. hr. The curettings showed enlarged and distorted glands lined by an atypical columnar epithelium manifesting anaplasia and mitoses. A neoplastic cellular stroma constituted 80 per cent of the tissue. The diagnosis was "carcinosarcoma of the uterus."

The patient was discharged from the hospital on March 7, 1939, and between March 18 and April 11, 1939, a total of 4,500 r of x-ray were delivered to the pelvis. However, death occurred on Aug. 8, 1939, approximately six and one-half months following the institution of therapy. Autopsy was not obtained.

CASE 2.—Mrs. D. A. S. (No. 456-831), a 47-year-old white nulligravida who had had the menopause ten years previously, was admitted to the hospital on April 15, 1943, complaining of vaginal spotting of fifteen weeks' duration, followed by two weeks of heavy flow including clots. Pelvic examination revealed the fundus of the uterus to be enlarged to approximately 8 by 10 cm. The uterus appeared to be irregular in outline, firm, pulled to the left, and fixed. A small papillary growth was observed on the right side of the external os of the cervix.

Curettings obtained on April 21, 1943, demonstrated a malignant mixed tumor arising from endometrial stroma and glands.

An exploratory laparotomy was performed on May 7, 1943. The uterus was found to be enlarged to the size of a ten weeks' gestation. On the left anterior surface, it was adherent to the tissues in the inguinal region. It was evident that the malignant process had already escaped the confines of the uterus and that extirpation would be useless. A biopsy of the involved peritoneal glands showed a structure similar to that seen in the primary tumor of the uterine cavity. The glandular elements dominated. In some regions the stroma was of a myxomatous character. The patient was discharged from the hospital on June 4, 1943.

Deep x-ray therapy was instituted, but she was unable to complete the prescribed course. Death occurred at home on Dec. 16, 1943, seven months after the diagnosis had been established.

CASE 3.—Mrs. A. G. S. (No. 526-096), a 58-year-old white gravida xvi was admitted to the hospital on Dec. 3, 1945, following two weeks of vaginal bleeding. Menopause had been artificially induced by radiation six years previously. Curettings obtained on December 10 contained tissue which was composed of irregular but quite typical cartilage, adjacent to which was a loose anaplastic fibrous tissue stroma. An irregular epithelial layer forming distorted acini in some places was present in the stroma. The diagnosis was carcinochondrosarcoma of the uterus. A total hysterectomy and bilateral salpingo-oophorectomy were performed on Dec. 14, 1945.

The patient was discharged to the tumor clinic on Dec. 28, 1945. She was hospitalized again (No. 574-418) from Aug. 8 to Aug. 28, 1946, because of severe pain in the right thigh and lower back.

The third hospital admission (No. 576-896) on Sept. 9, 1947, resulted from the appearance of a 2.5 cm. firm, round mass at the apex of the vagina. Biopsy of this mass was diagnosed as "anaplastic carcinoma, recurrent or metastatic." The patient was discharged from the hospital on Sept. 16, 1947. She was seen in follow-up clinic one month later, at which time the previously mentioned vaginal tumor was noted to have increased in size. A foul vaginal discharge was present. Death occurred on Nov. 18, 1947, at another hospital.

CASE 4.—Mrs. G. R. (No. 591-111), a 63-year-old white para ix, gravida x, was admitted to the hospital on March 7, 1948, with a complaint of leukorrhea and a questionable bloody vaginal discharge.



A diagnostic curettage was performed on March 8, at which time 3 c.c. of curettings were obtained, plus a polypoid structure measuring approximately 5 by 2 cm. The latter showed some areas of hemorrhage and appeared to be necrotic in some zones.

Fig. 1.

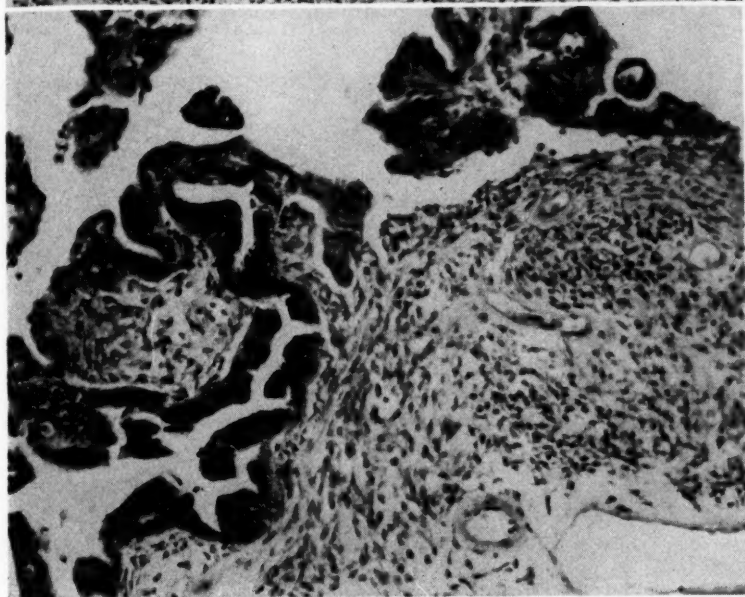
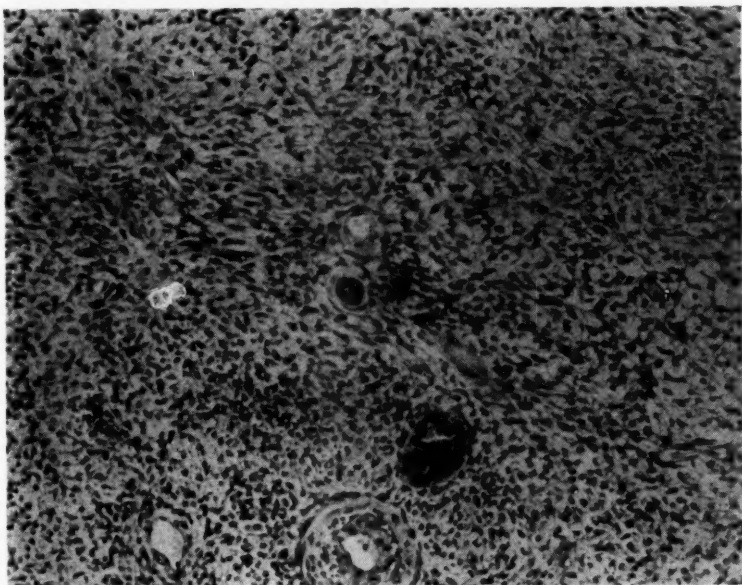


Fig. 2.

Fig. 1 (Case 2).—Curettings showing spindle-cell stroma embedded in which are atypical acini lined by columnar epithelium.

Fig. 2 (Case 2).—Metastatic nodule manifesting glandular elements with papillary arrangement and stroma of myxomatous character.

Sections from the base of the polyp showed a malignant tumor composed of two types of tissue, the greater part being composed of irregular spindle cells in a myxomatous

stroma with large numbers of tumor giant cells scattered throughout. In addition, there was a definite malignant epithelial type of tissue composed of cuboidal cells forming irregular glandular lumina and acini. The diagnosis was carcinosarcoma.

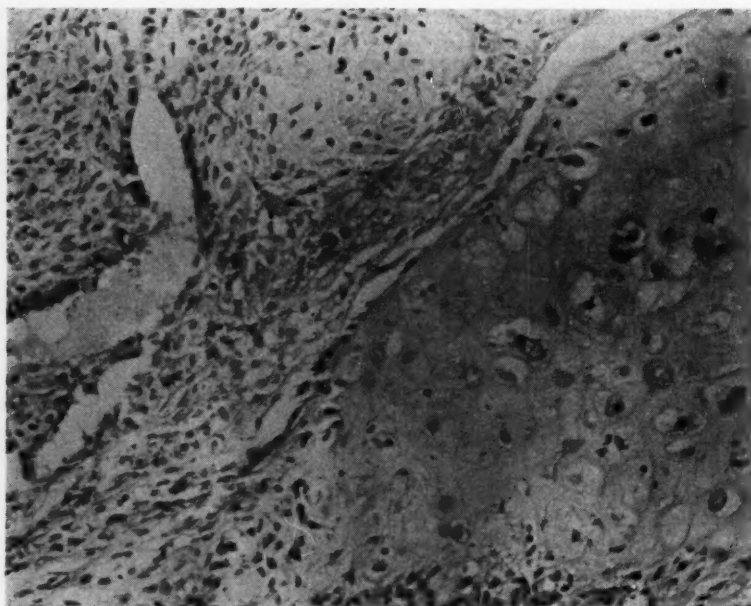


Fig. 3 (Case 3).—Curetings demonstrating typical cartilage in stroma.

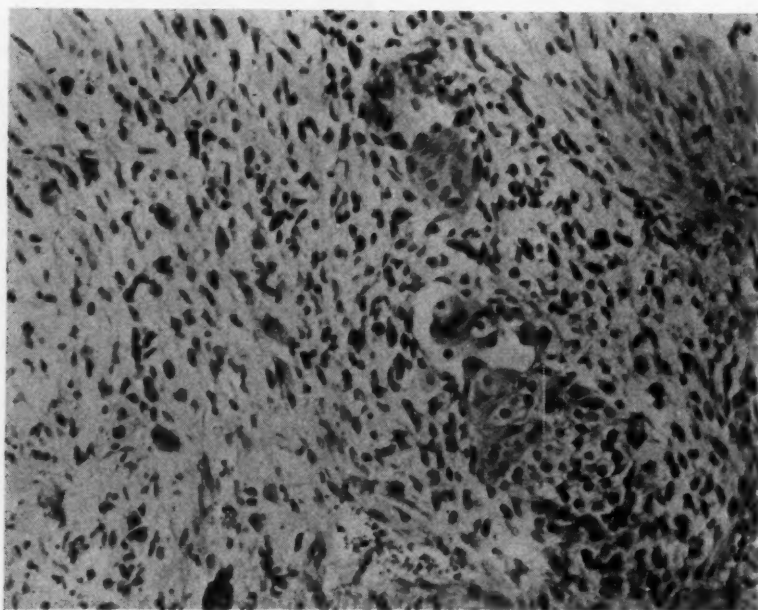


Fig. 4 (Case 4).—Tumor giant cells in sarcomatous stroma.

A total hysterectomy and bilateral salpingo-oophorectomy were performed on March 11, 1948. The uterus was enlarged to 15 cm. in diameter because of an intrauterine polypoid mass. Infiltration into the myometrium was evident. Sections through the parametrium showed extension of the tumor with invasion of venous channels.

The patient recovered from the operation and was discharged from the hospital. However, four months later, on July 6, 1948, she was readmitted (No. 601-663) complaining of abdominal enlargement, fatigue, and dyspnea of one week's duration. Death oc-

Fig. 5.

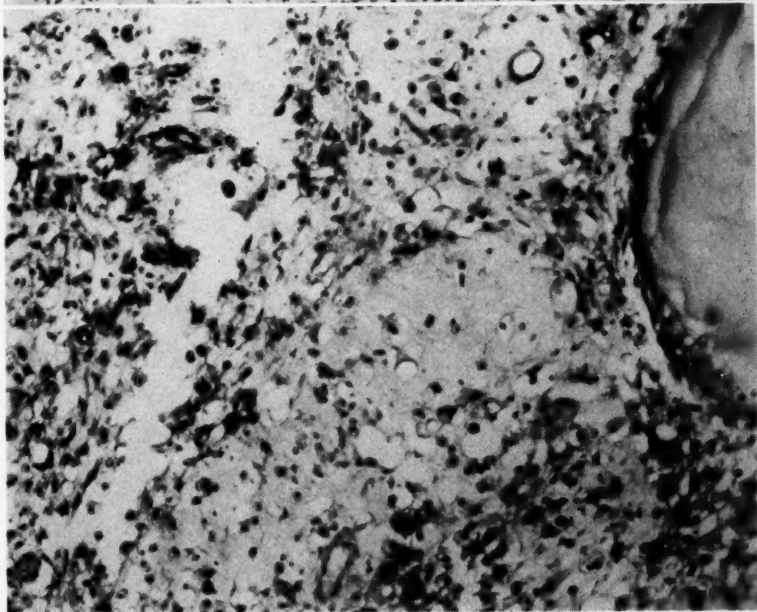
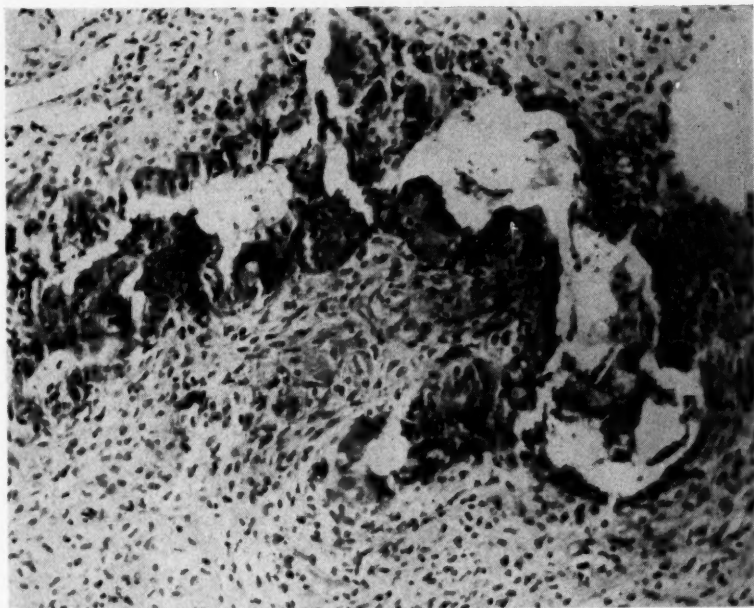


Fig. 6.

Fig. 5 (Case 5).—Adenocarcinomatous portion of tumor consisting of irregular glands lined by columnar cells evidencing anaplasia and mitoses.

Fig. 6 (Case 5).—Myomatous stroma resembling fetal cartilage.

curring on July 17. Postmortem diagnosis: (1) mixed mesodermal tumor of uterus (resected) with metastases of peritoneum, abdominal and mediastinal lymph nodes; (2) ascites; (3) diverticulosis of colon. Adenomatous polyp of colon.

CASE 5.—Mrs. G. K. (No. 592-915), a 69-year-old white nulligravida who had completed the menopause nineteen years previously, was admitted to the hospital on March 29, 1948. She had been examined by her physician on Feb. 23, 1948, at which time she stated that vaginal bleeding had been evident for ten months. Curetings showed a mixed malignant tumor composed in part of adenocarcinomatous tissue supported by a cellular stroma made up of polyhedral cells showing moderate anaplasia and mitoses. The histologic appearance was felt to be that of carcinosarcoma of the endometrium.

Between February 25 and the date of admission to the hospital, a total of 6,000 r of deep x-ray was administered to the pelvis. A total hysterectomy and bilateral salpingo-oophorectomy were performed on March 30, 1948. A 6 by 4 by 3 cm. pedunculated tumor was present in the endometrial cavity. Sections from the tumor showed a few zones in which the myxomatous tissue bore some resemblance to fetal cartilage.

The postoperative course was uneventful, permitting discharge from the hospital on April 9, 1948. As of Oct. 1, 1952, three and one-half years after operation, the patient was alive and well with no evidence of recurrence or metastasis.

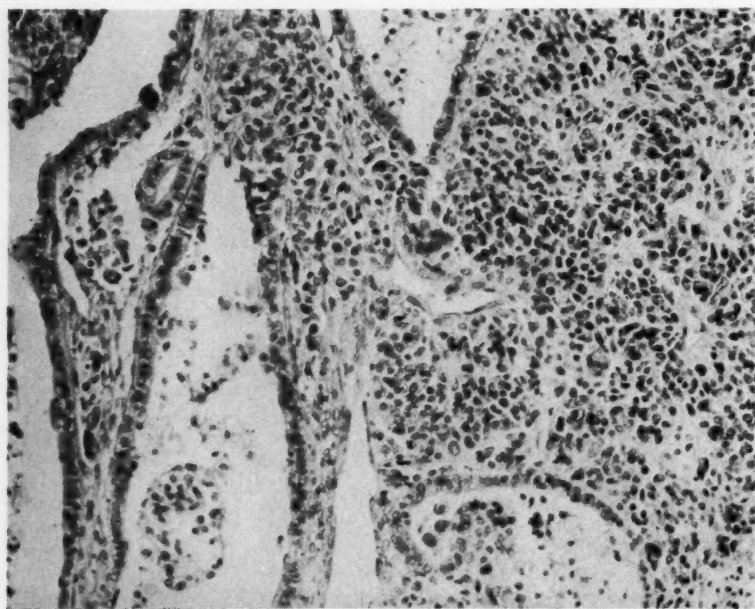


Fig. 7 (Case 6).—Section of uterine wall demonstrating glandular pattern of endometrium supported by stroma consisting of spindle-cell mass of undifferentiated cells having sarcomatous appearance.

CASE 6.—Mrs. E. G. (No. 656-880), a 60-year-old white para ii, gravida ii, was admitted to the hospital on June 18, 1950. She stated that the menopause had been induced with radium seventeen years previously. Approximately two months before admission, a slight colored vaginal discharge had been noted. Frank bleeding had commenced nine days before she entered the hospital.

No masses were palpated on pelvic examination. Gray-pink tissue was noted protruding through the external cervical os. Curetings obtained on June 20, 1950, were reported as mixed carcinosarcoma.

Total hysterectomy and bilateral salpingo-oophorectomy were performed on June 23. Sections from the uterus showed extensive invasion of the uterine wall by a tumor in which the cells in some regions were of a columnar type and had a glandular pattern. These were supported by a spindle-cell mass of undifferentiated cells which had a sarcomatous appearance.

Between June 30 and August 5, when the patient was discharged from the hospital, a total of 6,800 r of deep x-ray was delivered to the pelvis. She was readmitted to the hospital (No. 711-687) on Nov. 30, 1951, complaining of severe leg pain. This was presumed to result



from retroperitoneal spread of the tumor with involvement of the nerve roots. The patient was discharged from the hospital on Dec. 12, 1951.

On Dec. 31, 1951, she was admitted to a hospital in a neighboring city, where death occurred on Jan. 6, 1952, eighteen months following surgery.

Fig. 8.

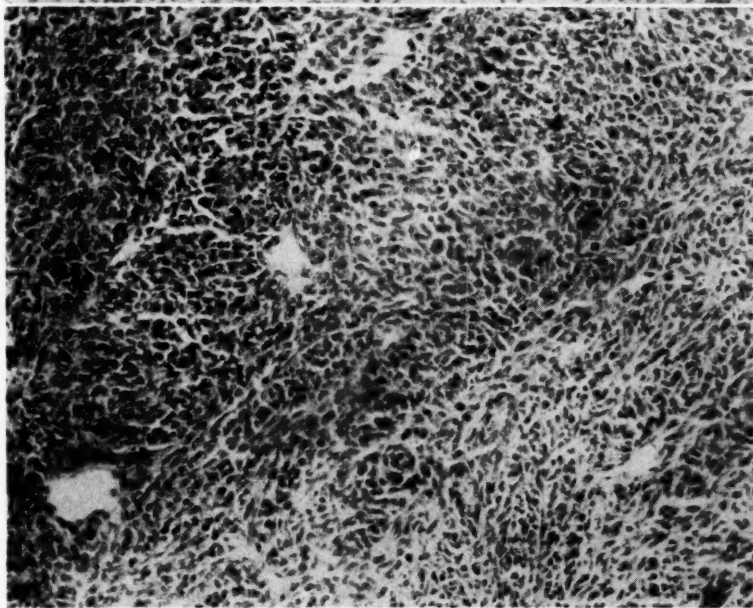
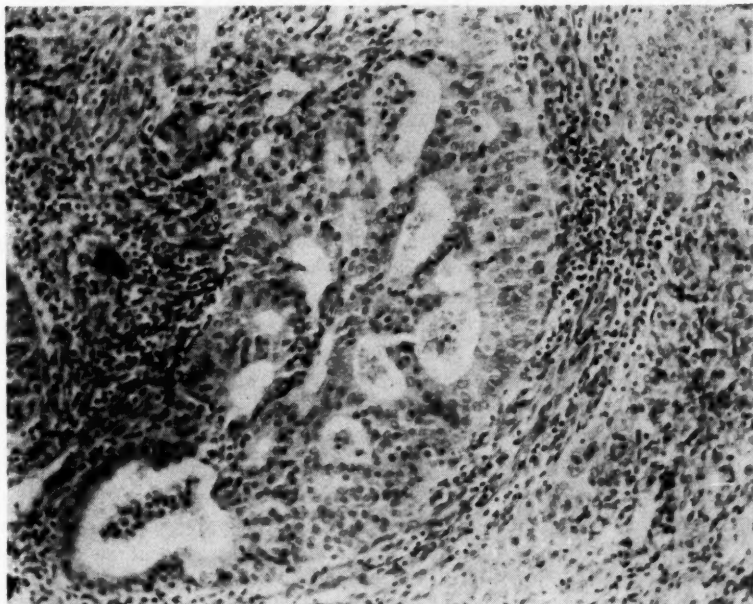


Fig. 9.

Fig. 8 (Case 7).—Section of metastasis showing carcinomatous element.

Fig. 9 (Case 7).—Curettings showing typical sarcomatous picture with interlacing bundles of spindle-shaped cells evidencing mitoses and anaplasia.

*Postmortem diagnosis:* "Carcinosarcoma of uterus with extension of tumor into pelvis, aortic lymph nodes, and soft tissue; tumor thrombus of right iliac vein; metastases to spine."

CASE 7.—Mrs. R. H. B. (No. 671-208), a 40-year-old white para iii, gravida iii, entered the hospital on Sept. 5, 1950, with a complaint of abdominal pain of one week's duration. The menses which had commenced at 13 years of age had been regular for fifteen years. Amenorrhea occurred abruptly and persisted for eight years. Scant irregular uterine bleeding which lasted only one or two days began at this time. The last menstrual period had occurred on July 31, 1950. On August 11, spotting appeared. However, a profuse vaginal hemorrhage occurred on August 18. A slight pink vaginal discharge was then present until the patient's admission into the hospital. One week previously, the patient suddenly experienced severe lower abdominal pain. Nausea and vomiting were absent. Slight pain was present upon micturition and defecation.

Tenderness was elicited when both lower abdominal quadrants were palpated. There was a tender mass in the midline of the lower abdomen and a questionable movable mass in the left lower quadrant. The presence of these masses was confirmed upon bimanual examination.

A diagnostic curettage was performed on Sept. 6, 1950, at which time a considerable quantity of suspiciously neoplastic-appearing tissue was obtained. The abdomen was then opened and a 5 cm. tumor mass was found replacing the left ovary. A similar mass about one-half the size replaced the right ovary. The masses were mobilized and the tissue composing them was found to be quite friable and grossly neoplastic in appearance. Frozen sections confirmed the impression that they were malignant. The sigmoid was adherent to the neoplasm, but the liver and mesentery appeared to be free of metastases. Total hysterectomy and bilateral salpingo-oophorectomy were performed.

A soft, raised cauliflower-like lesion measuring 3 cm. in diameter was present on the posterior wall of the endometrial cavity. Sections from this area showed a papillary adenocarcinoma. A typical sarcomatous picture with interlacing bundles of spindle-shaped cells showing frequent mitoses and moderate anaplasia was present in other areas. The carcinomatous element predominated in the metastases.

Deep x-ray therapy was instituted on the seventeenth postoperative day. However, after two treatments, the temperature rose to 102.5° F. and continued to spike to 101° F. daily. The therapy was discontinued. The clinical course progressed downhill rapidly, death occurring on Oct. 6, 1950, one month after operation.

*Autopsy:* The abdominal cavity was found to be filled with metastatic tumor, the entire omentum being replaced by a necrotic grayish-red friable tumor mass. The pelvis was filled with the tumor mass. Microscopic study of the metastases showed a picture of sarcoma rather than carcinoma.

CASE 8.—Mrs. I. N. (No. 728-606), a 65-year-old white para ii, gravida ii, was seen by me on Feb. 6, 1951, at which time she complained of two episodes of slight vaginal bleeding which had occurred during the two weeks prior to her visit to the office. During the preceding six months a profuse white vaginal discharge had been observed by the patient. The menopause had occurred twenty-four years previously.

Bimanual examination disclosed a uterus, which, though freely movable, was symmetrically enlarged to approximately twice the size that might be expected of a postmenopausal uterus.

The patient was admitted to the hospital on February 20. Ten c.c. of large, somewhat polypoid curettings were obtained on February 21. Sections showed a papillary arrangement of endometrial glands which were lined by large hyperchromic cells with anaplasia and mitoses. The stroma beneath was very cellular and actively proliferating with a moderate number of mitoses. This histologic picture was considered as that of carcinosarcoma of the endometrium.

On Feb. 26, 1951, nine Heyman capsules, each containing 10 mg. of radium, were inserted into the uterine cavity. The capsules were removed after 4,965 mg. hr. of radium had been delivered to the endometrium. The patient was discharged from the hospital on March 31, 1951.

She was readmitted on April 10, and on April 12 a laparotomy was performed. Upon entering the peritoneal cavity, it was apparent that the uterus had shrunk to one-half the size noted at the time of the curettage. The uterine wall was found to be intact, with no evidence

of breakthrough of the neoplasm. Metastases were not evident. A radical total hysterectomy with bilateral salpingo-oophorectomy and radical lymph gland dissection were effected according to the technique described by Meigs.<sup>17</sup>

Fig. 10.

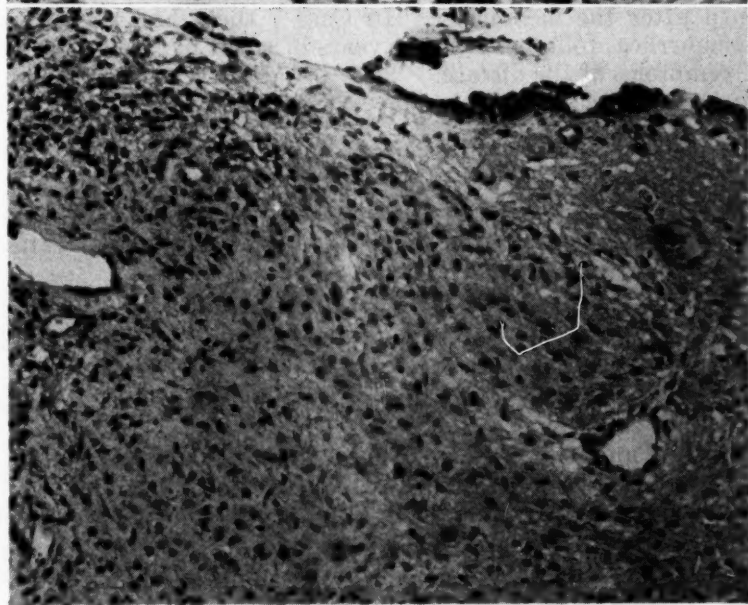
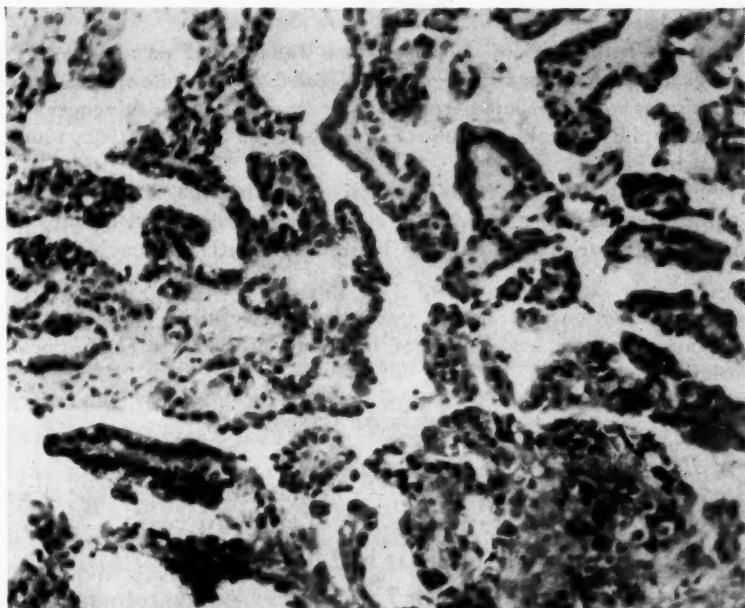


Fig. 11.

Fig. 10 (Case 8).—Curettings demonstrating endometrial glands with papillary arrangements. These are lined by large hyperchromic cells with anaplasia and mitoses.

Fig. 11 (Case 8).—Sections showing active proliferation of cellular stroma of endometrium.

Following a relatively uneventful postoperative course, the patient was discharged from the hospital on the eleventh postoperative day. Subsequent follow-up examinations showed no

evidence of recurrence of the disease. However, on March 28, 1952, nearly one year after operation, she complained of anorexia, abdominal distention, and weakness of one week's duration. A definite fluid wave was obtained when the abdomen was palpated.

Abdominal paracenteses were performed on April 10, 26, and May 10, at which 2,600, 4,000, and 4,800 c.c. of straw-colored fluid were withdrawn. Cytologic study of the fluid revealed the presence of cancer cells. On May 24, 1952, a paracentesis was repeated at which time 500 c.c. of foul-smelling purulent material were obtained.

The patient was readmitted to the hospital on June 7 with an abscess of the right abdominal wall. When incision and drainage were effected on the following day, approximately 1,000 c.c. of *B. coli* pus were evacuated from the abscess cavity. The subsequent clinical course of the patient was rapidly downhill, terminating in death on June 27, 1952, fourteen and one-half months following surgery.

At autopsy, there was evidence of generalized peritonitis. There were multiple 2 to 3 mm. seedlings of tumor over the omental surface and the serosal surface of the bowel. There were no large tumor masses and the liver was negative for evidence of metastatic carcinoma.

*Microscopic examination:* "Several sections of fatty tissue were obtained from the peritoneum showing cells with oval nuclei of irregular size. These cells appeared to be of mesenchymal origin."

### Analysis of Cases

1. *Age of Patient:* Average age 59 years.
 

40-49 years	2 cases	60-69 years	4 cases
50-59 years	1 case	Over 70 years	1 case
2. *Gravidity:* Six of the 8 patients had borne children.
3. *Relationship to Menopause:* In 7 of the 8 cases, symptoms did not become manifest until after the menopause. In Case 7 there had been an eight-year period of amenorrhea, followed by four years of scant irregular periods prior to the onset of symptoms of the disease.
4. *Radiation Previous to Symptoms:* Two cases: Case 3, 6 years; Case 6, 17 years.
5. *Genital Bleeding:* This symptom was present in all cases.
6. *Mortality:* Seven of the 8 patients had died within two years of treatment; 4 died within seven months of institution of definitive treatment. One patient is still alive after 3½ years.
7. *Relationship Between Mode of Treatment and Mortality:*
  - a. Case 1: Intracavitary radon plus deep x-ray therapy—died in six and one-half months.
  - b. Case 2: Exploratory laparotomy, postoperative deep x-radiation (incomplete)—died in seven months.
  - c. Case 3: Panhysterectomy—died twenty-three months later.
  - d. Case 4: Panhysterectomy—died four months later.
  - e. Case 5: Preoperative deep x-ray therapy (6,000 r), panhysterectomy—alive three and one-half years later.
  - f. Case 6: Panhysterectomy, postoperative deep x-ray therapy (6,800 r)—died eighteen months after operation.
  - g. Case 7: Panhysterectomy—died in one month.
  - h. Case 8: Preoperative intracavitary radium (4,965 mg. hr.), radical panhysterectomy with radical gland dissection—died fourteen and one-half months after surgery.
8. *Metastases:*
  - a. Unknown: 2 cases
  - b. Peritoneum: 4 cases



- c. Vagina: 1 case
- d. Aortic lymph nodes: 1 case
- e. Mediastinal lymph nodes: 1 case
- f. Spine: 1 case

### Comment

The status of carcinosarcoma of the endometrium ranges between two major viewpoints: (1) that of Willis, who has stated that, with the exception of sarcomatous change in the benign connective tissue of mammary fibroadenoma, he knows of no reported instance in which the interpretation of sarcomatous change in the stroma of an epithelial tumor can be definite and beyond doubt; and (2) that of Hill and Miller, who believe that the clinical course and pathological appearance of these tumors are sufficiently clear-cut to warrant their classification as a separate entity. We must, therefore, review the clinical course of carcinoma of the endometrium and compare it with the tumors under discussion to ascertain wherein the difference, if any, lies.

Ackerman and del Regato<sup>18</sup> stated that most carcinomas of the endometrium develop slowly and, even though the disease may be considerably advanced, the patients may survive for years in a rather good general condition. They emphasized the fact that the prognosis of carcinoma of the endometrium as a whole is a rather favorable one regardless of the method of treatment.<sup>19</sup> The authors quote Norman Miller, who reported that of 322 patients who consulted at The University Hospital, Ann Arbor, Michigan, a total of 301 received treatment, and of these, 194 (60 per cent) were well and free of symptoms five years later. They state further, that, in the past, three important facts seem to have found wide assent in the treatment of the disease<sup>20</sup>:

1. The best results are obtained when hysterectomy is practicable.
2. The results are considerably improved by preoperative radiotherapy.
3. A large proportion of the inoperable cases can be cured by a skillful application of radiation therapy.

It is important to state that these authors quote Healy to the effect that no institution should be satisfied with an over-all five year cure rate below 50 per cent.

Comparing these observations with those relative to the tumors being discussed, Hill and Miller noted that, in the latter, the course is invariably and rapidly fatal. The average duration of life was only six to twelve months after the onset of symptoms. No five-year survival in carcinosarcoma was recorded. Of the 8 cases herein reported, 7 patients had died within two years of the institution of treatment, while only one has survived three and one-half years (Case 5). In the cases reviewed by Hill and Miller, none showed any significant response to heavy radiation. Our experience at the Hartford Hospital was similar, in that it appeared that, regardless of the form of therapy employed, the termination was the same—death within a relatively short time. It is quite apparent that the results in these cases differed markedly from the usual experience with carcinoma of the endometrium, even though the therapy utilized was practically the same for both types of tumors.

Another dissimilarity between the two types of tumors, though perhaps not of great significance, is one observed by Willis<sup>4</sup> who found that endometrial cancer often occurs in the single and nulliparous. In our series, all of the patients had been married, and 6 of the 8 had borne children. Of the 4 cases reported by Hill and Miller, only one patient was a nullipara.

Following Hill and Miller these additional observations may be made:

1. A history of previous radiation to the uterus for supposedly benign conditions was far too prevalent in the reports of carcinosarcomas to be accepted as purely coincidental. In 4 of 13 cases collected by Lisa, Hartmann, Bayer, and Bonar; in 3 of 4 cases reported by Hertig and Sommers<sup>21</sup>; in the case reported by Walter and Mintz<sup>22</sup>; and in 2 of the 4 cases of Hill and Miller radiotherapy to the uterus had been given several years before the onset of the malignancy. In our series, 2 of the 8 patients had received similar therapy, one six years and the other seventeen years before the onset of symptoms of the disease.

2. Corporal carcinosarcomas occurred most frequently in the same age group as do the usual endometrial carcinomas, namely between the ages of 55 and 65. The average age for the 8 cases presented herein was 59 years.

3. There was no significant difference in symptoms between these and other uterine malignancies. Genital bleeding, which was present in all of our cases, is the usual complaint. The physical findings are usually limited to that of an enlarged uterus, although in rare instances, as in one of our cases, tumor may be seen protruding from the cervix.

4. Grossly, the tumors have a rather characteristic appearance. There may be one or more polyps projecting into the uterine cavity. These polyps may be either sessile or pedunculated, and arise more often than not from the posterior wall of the uterus. They can be differentiated from submucous leiomyomas by their softer consistency, fleshy appearance, and smooth, glistening cut surface. Myometrial invasion is variable. This was present in one-half of our cases.

5. Microscopically, a variety of tissue has been observed in the sarcomatous portion of the tumor, including striated muscle, smooth muscle, cartilage, bone, fat, osteoid tissue, fibrous tissue, and myxomatous tissue. Not all of the neoplasms will necessarily contain more than one of these elements.

6. Local recurrence and metastases are the usual sequelae to carcinosarcoma. Distant metastases are less frequent, but the lungs and pleurae are the chief sites when they occur. In 6 of our 8 cases, metastases occurred relatively early after the onset of the disease. However, Willis<sup>5</sup> states, to the contrary, that, in general, endometrial carcinoma metastasizes late.

### Summary

It is apparent from the foregoing review that a controversy exists as to whether carcinosarcoma of the endometrium is a distinct clinical entity or merely a variation of the usual carcinoma of the endometrium. The opinions of eminent authorities like Willis and Novak, who incline to the latter theory, cannot be disregarded. It is their belief that the histologic appearance of the

tissue in these cases is the result of sarcomatous metaplasia secondary to exudation and inflammation which accompany tumors of the endometrium. On the other hand, evidence has been recorded by other astute observers to the effect that a malignant endometrial neoplasm exists which differs from the commonly occurring variety of adenocarcinoma both in pathology and clinical behavior, especially in its rapidly fatal course, despite the institution of all forms of therapy which have had fairly favorable results in the management of carcinoma of the endometrium.

After a review of the evidence, it would seem in the interest of clarity that the diagnosis of "carcinosarcoma" should be deleted from the nomenclature and a separate category of "pleomorphic carcinoma" recognized as a distinct subdivision of carcinoma of the endometrium. Thus, whenever sarcomatous metaplasia is noted histologically, one might anticipate a clinical course entirely different from that which is usually associated with adenocarcinoma of the endometrium. The usual forms of treatment (x-ray, radium, hysterectomy) which have a moderate success in the usual case of adenocarcinoma of the endometrium could not be considered as equally efficacious in those of what may be recognized as "pleomorphic carcinomas." Whatever the treatment in such cases, the inevitable prognosis would appear to be rapid metastases with a fatal termination within a relatively short period.

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## AN EVALUATION OF DIFFERENTIAL STAINING TECHNIQUES IN CANCER CYTOLOGY\*†

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THE use of the Papanicolaou technique to stain cervical cell scrapings has given preparations which are excellent for diagnostic study. The Papanicolaou stain reveals clearly the form and the size of the cells, the concentration and distribution of chromatin in the nucleus, and the acidophilic or basophilic reaction of the cytoplasm. Consequently, this method of staining has achieved wide acceptance in diagnostic endocrine studies as well as in the study of cancer.

Despite its many advantages, the Papanicolaou procedure does not tell us all we would like to know about the histochemistry of the cells. In fact, no single staining procedure can do so. We have, therefore, turned to the use of five additional stains to supplement the Papanicolaou technique, and to aid us in studying the metabolic changes in cervical cells, as they pass from normal, to precancer, to frank malignancy.

The five staining procedures we are now using are: (1) the modified Best's carmine stain for glycogen, (2) the silver staining technique of Hortega, (3) the peroxidase stain, (4) the alkaline phosphatase stain, (5) the Feulgen stain.

1. *The Modified Best's Carmine Stain for Glycogen.*<sup>1, 2</sup>—In this procedure, the nuclei are first stained with hematoxylin. After rinsing with 1 per cent acid alcohol, the carmine stain is then applied. Following this technique, the nuclei appear deep blue in color due to the staining with the hematoxylin, while the glycogen granules in the cytoplasm appear a brilliant red. As a rule, in mature, cornified cells with pyknotic nuclei, one finds a high concentration of glycogen granules in the cytoplasm. The cytoplasm of cells with vesicular nuclei usually contains less glycogen, although there are exceptions to this rule. The cells of the vaginal epithelium contain high concentrations of glycogen during sexual maturity and while ovarian function is at a high level. During menopausal or surgical atrophy, or during the functional hypoestrinism of childhood, the glycogen content of the cells of the vaginal epithelium is low. In atrophic vaginal mucosal cells, administration of estrogen will cause an increase in the amount of glycogen present, thus indicating that the formation of glycogen depends, at least in part, on the presence of estrogen. In pregnancy, the glycogen content of these cells rises even higher.

In inflammatory cell types (Grade I) the glycogen content of the cells shows a slight decrease. In precancer (Grade II) as in fully developed cancer

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cells (Grade III), the glycogen content is usually zero. The degree of decrease is dependent on the stage of malignancy.

2. *The Silver Staining Method of Hortega*.<sup>3, 4</sup>—This technique was first used by Hortega to demonstrate fine details of structure of cells of the nervous system. It is based on the precipitation of silver from an alkaline ammoniacal solution. Such a precipitation can be brought about either by substances with a high reducing potential (such as ascorbic acid, or conjugated unsaturated ketones, or aldehydes) or by inorganic ions. By this technique, the nucleus appears yellow brown to black, depending on the chromatin content and the duration of the staining procedure. The cytoplasm is either yellow brown or gray, depending on the pH of the cytoplasm when stained. Most of the concentrations of inorganic ions in the cells are colored by this silver stain technique. As compared with the normal cell, the malignant cell has a darker nucleus, and the cytoplasm may be either lighter or darker.

3. *The Peroxidase Stain*.<sup>5</sup>—In this procedure, benzidine is oxidized, when peroxidase enzymes are present, by hydrogen peroxide to produce a deep blue or brown color. The leukocytes of the blood give a characteristic benzidine reaction, showing bright blue granules in the granulocytes. This method has not hitherto been used in the study of cells obtained in cervical scraping. Normal cells obtained by scraping do not give the benzidine reaction with this procedure. We are inclined to ascribe a slightly positive reaction to the nuclei of cancer cells, although the decision is a difficult one because of the very dark color seen in cancer nuclei when they are counterstained with hematoxylin and eosin. Further studies using this technique are under way.

4. *The Alkaline Phosphatase Reaction*.<sup>6, 7</sup> (Gomori's Technique).—In this study, the fixed slide is immersed in a substrate consisting of a buffered (barbital) alkaline substrate containing sodium glycerophosphate, calcium chloride, and magnesium sulfate as a catalyst. At the end of three hours, the slide is rinsed, a solution of cobalt chloride is added, and, after rinsing, a solution of ammonium sulfide is added. The presence of phosphatase enzyme is denoted by the development of a black color due to the precipitation of cobalt sulfide. In normal cells the alkaline phosphatase reaction is slight or absent. There is usually slight staining of the nucleus and cytoplasm. However, cancer cells show a striking increase in the alkaline phosphatase reaction of both nucleus and cytoplasm, most pronounced in the nucleus. Cancer and precancer cells may, therefore, be recognized by their greatly increased content of alkaline phosphatase. There is a gradual increase in alkaline phosphatase as we ascend the series from normal to precancer to cancerous cells. The more malignant the cells, the higher the concentration of alkaline phosphatase.

5. *The Feulgen Stain*.<sup>8, 9, 10</sup>—The Feulgen stain is based on the Schiff reaction for aldehydes. It is used to detect the presence of desoxyribonucleic acid, by acid hydrolysis of the nucleoproteins, followed by application of the Schiff reaction to the cell. The desoxyribose liberated on hydrolysis is stained dark red by leukofuchsin, and indicates the presence in the cell of desoxyribonucleic acid from which the pentose was liberated. The counterstain used is fast green. As far as we know, this reaction has not yet been applied to vaginal smears and cervical scrapings, although Pollister<sup>10</sup> has studied the concentration of desoxyribonucleic acid in these cells by ultraviolet spectroscopic examination. We are using a modification of the Feulgen stain described by Longley,<sup>11</sup> which has given excellent results in our hands.

With the use of this technique, normal pyknotic vaginal epithelial cells show an intense dark red coloration of the nucleus, with a deep blue-green color in the cytoplasm. Cancer cells show a decreased concentration of red

color in the nucleus, although the total *amount* may be greater due to the increased nuclear size. The cytoplasm of malignant cells is distinctly paler in color than of normal cells.

The stain, as used in our hands, colors the cytoplasm of the basal cells a deep blue green and the nucleus a dark red, giving the impression that the nucleus contains considerable desoxyribonucleic acid. With the maturing of the cell, the concentration of DNA in the nucleus decreases, as does the blue-green color of the cytoplasm. This progressive lightening in color reaction continues until full maturation of the cell in the highly cornified cell has been achieved. The small pyknotic nucleus then gives a deep red color, showing a high concentration of DNA in a small nuclear volume, while the green coloration of the cytoplasm again begins to increase. Here and there, in the mature cell, small red particles are visible in the cytoplasm as either dust or mitochondria.

Cancer cells differ from normal cells. In their nuclei, the concentration of DNA is less, although, due to the greater size of the nucleus, the total amount of DNA is probably increased. No red particles are ever visible in the cytoplasm which shows a pale blue-green color throughout, indicating poor cytoplasmic development, and leaving the impression that there is a disturbance in the nuclear-cytoplasmic relationship particularly in regard to their metabolism of DNA.

#### Discussion

It may not be difficult for an experienced cytologist to diagnose a slide as definitely normal, or frankly malignant. However, the gap between normal cells and cancer cells includes many gradations, the exact differentiation of which is a difficult task where difference of opinion is widespread. Yet, an exact grading of the cancer stage by precise cell analysis is of greatest importance for diagnosis, prognosis, and therapy, and every effort should be made to further this purpose.

Ayre contributed to a better knowledge of cytology by an exact grading from normal cells and inflammatory cell types via the precancer cell complex to the carcinoma in situ and cancer cells. His concept is of great practical value, because we are now able to make follow-up behavior studies of the cells in our patients and follow the cancer process in its developmental stages.

The group of cells referred to as the precancer cell complex of Ayre has the following features:

1. A persistent high concentration of cornified cells in the cervical scraping.
2. Precocious cornification.
3. Cell gigantism.
4. Large hyperactive and immature nuclei with hyperchromatic staining.
5. Multilobulation and multinucleation of nuclei in all layers of the squamous epithelium.
6. Hyperplastic basal cells.
7. Perinuclear halo.

Dr. W. Burton Ayre suggested the inclusion of cell dwarfism consisting of small very active most acidophilic basal cells with high chromatin content and irregular size and form.

I believe that hypercornified cells without nucleus (or only a shadow of nucleus, giving a pale yellow coloration with the Papanicolaou stain) may also be included in this concept. We very often found in our follow-up studies of precancer patients who reacted favorably with administration of medications that a possible recrudescence was accompanied by appearance of cell dwarfs and hypercornification of the mature cells. Whether these recurrences were caused by higher estrogen content or were only accompanied by it—or even opposed by it in an effort at self defense—is not known.

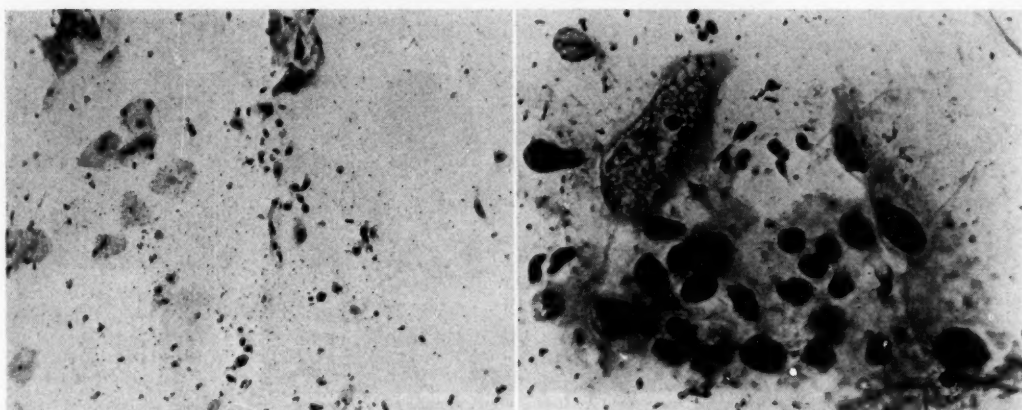


Fig. 1.—Left, Best's carmine stain. Normal cells upper left, precancer cells to the right. ( $\times 150$ . Reduced one-fifth.)  
Right, Best's carmine stain. The normal cell to the left, the precancer cells to the right. ( $\times 600$ . Reduced one-fifth.)

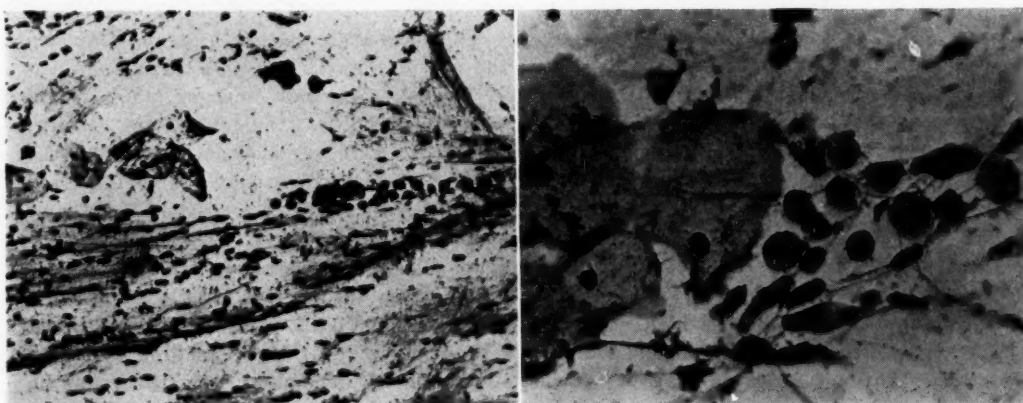


Fig. 2.—Left, silver stain. Normal cells to the left, precancer cells to the right. ( $\times 150$ . Reduced one-fifth.)  
Right, silver stain. Normal cells to the left, precancer cells to the right. ( $\times 600$ . Reduced one-fifth.)

As a matter of routine, we now apply all five of these new color reactions to all slides taken on research patients, since we feel that, in this way, we may learn more about the functional state of the exfoliated cells. From the morphological viewpoint, it may be that these additional stains will provide aid in diagnosis and in recognition of abnormal cells. However, in this study we are primarily concerned with pointing out those aspects of the metabolism

of the normal and malignant cell which are emphasized by the differential staining techniques, and especially with studying the metabolic alterations of cells in their environment. A third point that may be made is that the new stains may provide a means for following more closely the course of clinical precancer and clinical cancer, as well as the effects of our attempts at therapy. We can study the effects of such variables as the administration of hormones, drugs, or chemicals, systemically or locally.

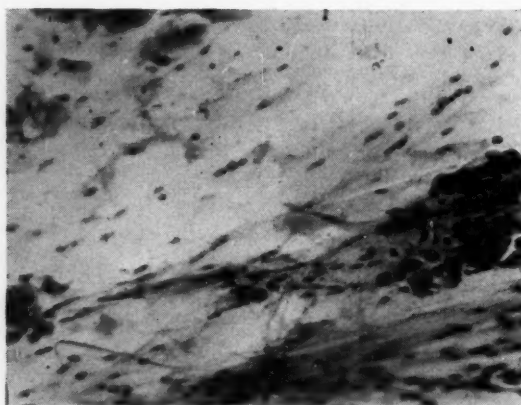


Fig. 3.—Peroxidase stain. Normal cells to upper left, precancer cells to the right in the middle. ( $\times 150$ . Reduced one-fifth.)

A single case history may be used to exemplify this point:

Mrs. T, a 44-year-old woman, came to us in December, 1951, with symptoms of excessive bleeding at the time of menstruation. The patient, a mother of three children, had a small laceration on the superior lip of the portio vaginalis. Gynecologic examination revealed retroversion of the uterus which, however, was not enlarged. The portio was somewhat irregular, but no patches or erosions were visible. The cells of the cervical surface scraping showed anaplastic precancer cells, with a few cells characteristic of the carcinoma in situ stage (Grade 2B-3A of our grade system). Figs. 1 to 5 may illustrate some features of the slides of this patient taken at the same moment, colored in 5 different ways. Fig. 1 shows a Best's carmine stained slide, low and high power. Normal cells present a large amount of glycogen, the abnormal cells with hyperactive irregular nuclei contain no glycogen or only a slight amount. Very often the nucleus is only surrounded by a shadow of cytoplasm which contains no glycogen. Fig. 2 shows a silver stained slide, low and high power. The nucleus has a brown to black color depending upon the pyknosis. The cytoplasm is gray or brown yellow colored, depending upon the grade of cornification. In precancer cells the color of the nucleus is darker, and form, size, and chromatin content are distinctly visible. The cytoplasm in the cancer cells is lighter or darker colored than in normal cells, showing an irregularity and imbalance of inorganic ions as compared to normal cells. Fig. 3 shows the peroxidase reactions. Neither the cytoplasm of cancer cells nor that of normal cells shows distinct peroxidase granules as appear in the leukocytes. We are uncertain whether the nucleus of the cancer cell is oxidase positive, the darkness of the nucleus precluding close examination. Fig. 4 shows the alkaline phosphatase reaction, low and high power. Cancer cells contain much more alkaline phosphatase than normal cells. This is especially noticeable in the nucleus. Fig. 5 shows the Feulgen reaction, low and high power. The photomicrograph shows a decreased concentration of the red formation in the nucleus in precancer cells though the total amount may be greater. The cytoplasm very often shows only a shadow or a very pale



blue green. Three months later, the vaginal epithelium of the patient showed a marked improvement. She had received 720 B suppositories during that time.

A summary of the cytologic characteristics noted in the use of these five different stains in cancer cytology is shown in Table I.

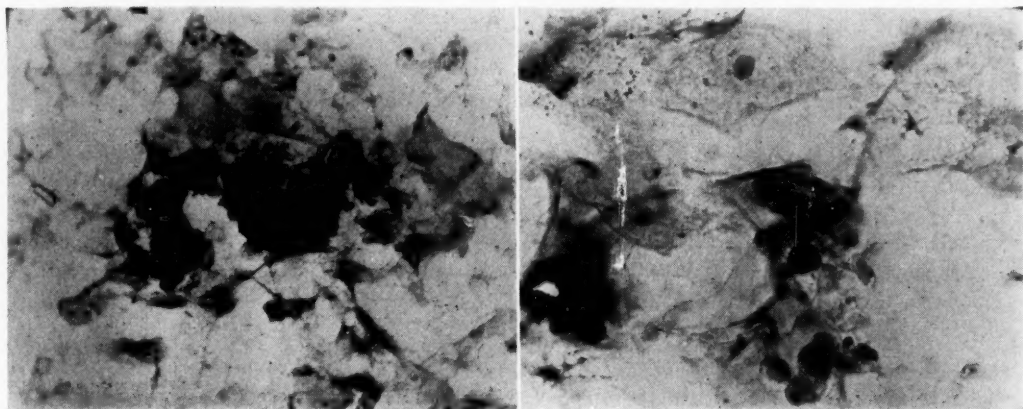


Fig. 4.—Left, alkaline phosphatase stain. Normal cells upper middle, precancer cells in the center. ( $\times 150$ . Reduced one-fifth.)

Right, alkaline phosphatase stain. Normal cells at the top, precancer cells in the center. ( $\times 600$ . Reduced one-fifth.)

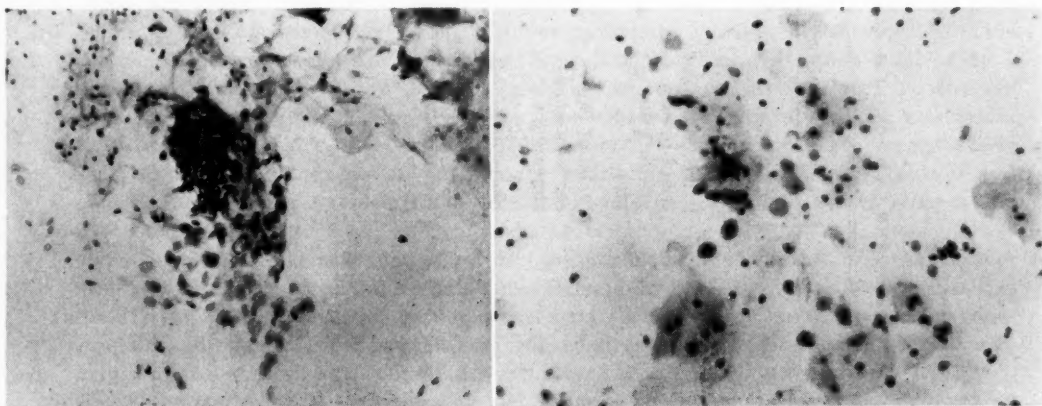


Fig. 5.—Left, Feulgen stain. Normal cells at the top, precancer cells in the center. ( $\times 150$ . Reduced one-fifth.)

Right, Feulgen stain. Normal cells dispersed to the side contain Feulgen-positive mitochondria, precancer cells in the center contain only a small rim of cytoplasm. ( $\times 600$ . Reduced one-fifth.)

### Staining Techniques

A summary of our staining techniques is given below:

#### 1. Glycogen Stain

1. Smears fixed in 95% alcohol.
2. Rinse in 70% alcohol (6 rinses).
3. Stain in Ehrlich's acid hematoxylin for 20 minutes.
4. Rinse in 50% alcohol (8 rinses).
5. Differentiate in 1% acid alcohol (8 rinses).
6. Rinse in 50% alcohol (8 rinses).
7. Stain in Best's carmine for 20 minutes.

TABLE I. SUMMARY OF THE CYTOLOGIC CHARACTERISTICS IN CANCER CYTOLOGY

	GLYCOGEN		SILVER		PEROXIDASE		ALKALINE PHOSPHATASE		FEULGEN STAIN	
	CYTOPLASM	NUCLEUS	CYTOPLASM	NUCLEUS	CYTOPLASM	NUCLEUS	CYTOPLASM	NUCLEUS	CYTOPLASM	NUCLEUS
Normal	Dependent on age, day of cycle, cornification ++	-		+	Results are not yet clear, leukocytes contain brown yellow granules	±	±	±	Sometimes very small as dust or mitochondria stain	+
Inflammatory	+	-		+	Nuclei of cancer cells sometimes show a blue color to peroxidase	±	±			++
Precancer	±	-	In precancer and cancer cells the concentration is irregular	++	This reaction requires further study	+	+	+	-	++
Cancer	-	-	The amount is less and because there is less cytoplasm	+++ The nucleus contains more stain in cancer cells in concentration and volume		+++ The nucleus contains more stain in concentration and volume	+++ The cytoplasm contains in cancer cells more stain in concentration, less in volume	+++ The nucleus contains in cancer cells more stain in concentration and volume	- The cytoplasm contains in cancer cells less stain in concentration and volume	+++ The nucleus contains in cancer cells more stain in volume, less in concentration

8. Rinse in two changes of pure methyl alcohol (8 rinses).
9. Rinse in absolute ethyl alcohol.
10. Clear in xylol and mount.

*Best's Carmine Stock Solution*

Carmine 2 Gm.  
Potassium carbonate 1 Gm.  
Potassium chloride 5 Gm.  
Distilled water 60 ml.  
Boil gently—add 20 ml. concentrated ammonium hydroxide.

*Best's Carmine Staining Solution*

40 ml. stock solution  
120 ml. pure methyl alcohol  
60 ml. ammonia

Change staining solution every week regardless of how often stain is used. Change hematoxylin every 6 weeks to 2 months. 1% acid alcohol is made by adding 1 ml. of concentrated HCl to 99 ml. 70% alcohol.

2. *Silver Stain*

Fixation of smears: The smear, while still moist, is immersed in 20% formalin (1 volume formaldehyde diluted with 4 volumes distilled water) for at least 15 minutes. The smears may be allowed to dry following fixation or carried directly to the next solution.  
*Staining Procedure:*

1. Rinse smears in ammonia water (5-6 drops ammonium hydroxide in 100 ml. distilled water).
2. Rinse successively in 2 jars of distilled water.
3. Impregnate with a medium strength silver carbonate solution for 2 minutes. This dilution of silver carbonate is prepared by adding 1 volume of stock solution to 1 volume of distilled water. The stock solution is prepared as follows: To 100 ml. 10% silver nitrate, add 300 ml. 5% sodium carbonate. Then carefully add ammonium hydroxide drop by drop (about 10 ml.) with constant shaking until the precipitate is just dissolved. An excess of ammonium hydroxide will reduce impregnation and should, therefore, be avoided. This solution should be stored in a brown glass bottle protected from light.
4. Remove excess silver carbonate solution by touching edge of slide to absorbent paper and reduce in 1% formalin (1 ml. 40% formaldehyde diluted with 39 ml. distilled water) for 1 minute. Although not a necessary part of the procedure, a lighter background, and one with few particles of reduced silver, will be obtained if the formalin solutions for fixation and reduction are buffered to a pH of approximately 7.
5. Rinse thoroughly in distilled water and examine under the microscope for staining quality. In the event that a heavier impregnation is desired, cover the slide again with silver carbonate solution for 2 to 3 seconds, reduce once more in 1% formalin, and rinse in distilled water.
6. Dry in air or by rinsing successively in 90% and absolute alcohol, rinse in xylol, and mount in clarite or Canada balsam.

We prefer to color only two minutes with silver carbonate instead of the customary three minutes because the staining of the nucleus thus obtained gives more readily observable gradations in stain intensity.

3. *Peroxidase Stain*

1. Smears are fixed in 20% formalin (1 volume formaldehyde diluted with 4 volumes distilled water).
2. Plunge in water for a few seconds and remove excess water.
3. Apply Benzidine Reagent for 5 minutes.
4. Transfer to water for 5 minutes.
5. Stain with Harris hematoxylin for 2 minutes.
6. Rinse in water 1 minute.

7. Stain with 0.1% eosin for 20 seconds.
8. Dehydrate in 95% alcohol for 30 seconds.
9. Absolute alcohol 5 seconds.
10. Clear in xylol.
11. Mount in balsam.
12. Run controls in which benzidine is omitted.

*Benzidine Reagent*

Dissolve 1 Gm. benzidine in 250 ml. 80% methanol and add 20 drops 3% hydrogen peroxide. Dilute with 1 to 2 volumes distilled water before using. Store in the dark.

4. *Alkaline Phosphatase Substrate*

- 40 ml. 5% sodium barbital
- 20 ml. 2% sodium glycerophosphate
- 5 ml. 2%  $\text{CaCl}_2$
- 2 ml. 2%  $\text{MgSO}_4$
- 30 ml. distilled water

Adjust to pH 9.5.

1. Smears are fixed in alcohol 80% or acetone.
2. Without drying, immerse in substrate and incubate for variable period of time up to 3 hours or more. Note time in fixative and time in incubation.
3. Pour off substrate and wash gently with tap water for 5 minutes.
4. Pour off tap water. Place in 2%  $\text{CoCl}_2$  for 2 minutes.
5. Wash successively in 3 washes of distilled water. Wash 3 times in each beaker.
6. Pour in 1% solution of  $(\text{NH}_4)_2\text{S}$  for 1 minute. (If enzyme is present, material turns black here.)
7. Pour off  $(\text{NH}_4)_2\text{S}$  and rinse in tap water 2 or 3 times.
8. Series of alcohol to dehydrate: 70%—95%—to absolute.
9. Xylol.
10. Mount.

5. *Feulgen Stain*

Preparation of leukofuchsin solution: Without heating, dissolve 0.5 Gm. of basic fuchsin in 100 ml. of 0.15 N HCl to which 0.5 Gm. of  $\text{K}_2\text{S}_2\text{O}_8$  (or  $\text{Na}_2\text{S}_2\text{O}_8$ ) has been added. When the solution is no longer reddish (2 or 3 hours) decolorize by shaking with 300 mg. of freshly activated charcoal for 2 minutes and filter through Whatman No. 2 paper or the equivalent. The reagent is ready for immediate use, and if stored under refrigeration may be preserved for months.

1. Smears are fixed in a mixture of 1 part 95% alcohol, 1 part saturated  $\text{HgCl}_2$  solution.
2. Rinse 1 minute in 1N HCl.
3. Place in 1N HCl at 50° C. for 20 minutes.
4. Rinse 1 minute in cold 1N HCl.
5. Immerse 2 hours in leukofuchsin solution.
6. Rinse for 3 successive 10 minute treatments in acid sulfite solution.
7. Wash 5 minutes in tap water.
8. Rinse in distilled water.
9. Counterstain in 0.002% alcoholic fast green FCF  $\frac{1}{2}$  minute.
10. Dehydrate in alcohols and xylene.
11. Mount.

(Control smears omitting steps 2 to 4 should run together with the Feulgen stain.)

Acid sulfite solution is composed of 6 ml. 10% potassium metabisulfite (or sodium bisulfite), 6 ml. normal hydrochloric acid, and 120 ml. distilled water.

This procedure is a slight variation of that usually used. For one thing we color only 30 seconds with fast green instead of 3 minutes. Too intense a staining with the fast green interferes with the clarity of the red color in the nucleus produced by the fuchsin, and



we have found that a shorter interval of counterstain allows the red fuchsin to appear clearly while not interfering with adequate cytoplasmic detail.

### Summary and Conclusions

A description has been given of cancer and precancer cells in relation to the following applications:

1. Five stain techniques and their application to the study of cervical cell scrapings.
2. Normal, precancer, and cancer cell staining.
3. Serial cell behavior studies in relation to structural morphology and therapy.
4. Desoxyribonucleic acid studies in Feulgen staining techniques in relation to the stage of cancer.

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## **SQUAMOUS-CELL CARCINOMA ARISING IN BENIGN CYSTIC TERATOMA OF THE OVARY: A REPORT OF THREE ADDITIONAL CASES AND REVIEW OF THE LITERATURE**

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**P**PRIMARY squamous-cell carcinoma arising in a benign cystic teratoma (dermoid cyst) of the ovary is a rather uncommon neoplasm. Only 60 cases have been reported in the literature which are acceptable on the basis of gross and microscopic description and appropriate photomicrographs. The classical paper on the subject is that of Masson and Ochsenschlitz<sup>1</sup> in 1928 from the Mayo Clinic. They reviewed the entire literature and found only 33 acceptable cases, to which they added 3 cases of their own. The others reported were rejected either because of inadequate and incomplete description or because they were not considered to be bona fide cases. Other subsequent acceptable cases include one reported by Ascanio-Suarez<sup>2</sup> in 1929, one by Deaver<sup>3</sup> in 1931, one by Delaney<sup>4</sup> in 1931, 4 additional ones from the Mayo Clinic by Counseller and Wellbrock<sup>5</sup> in 1934, 4 by Kent<sup>6</sup> in 1936, one of his own and a review of 5 additional cases in the European literature by Bowles<sup>7</sup> in 1937, one by Fein and Hobart<sup>8</sup> in 1937, one by Cardwell and Pund<sup>9</sup> in 1938, one by Willis<sup>10</sup> in 1937, one by Meiklejohn and Stallworthy<sup>11</sup> in 1938, one by Brody<sup>12</sup> in 1941, one by Williams and Bloom<sup>13</sup> in 1942, and one additional case by Willis<sup>14</sup> in 1948. Additional cases are merely mentioned in articles written on other primary subjects and, lacking full description and adequate photomicrographs, are not considered to be acceptable cases by this author until published in detail at some future date. One case is mentioned by Jones during a discussion of Counseller and Wellbrock's<sup>5</sup> paper, three by Falk in a personal communication to McCullough and associates<sup>15</sup> in 1946, one by Randall and Hall<sup>16</sup> in 1952, and one by Silverman and Alban<sup>17</sup> in 1952. Other cases undoubtedly exist which have never been submitted for publication. The addition of the 3 cases now being reported brings the total in the literature to 63.

### **Report of Cases**

**CASE 1.**—Mrs. L. M., a 47-year-old white woman, entered the Illinois Masonic Hospital, Chicago, Ill., on June 27, 1949, complaining of pain and fullness in the right lower abdomen for the past few weeks and gradual enlargement of the abdomen for an undetermined period of time. Physical examination revealed a large mass, filling the hypogastrium up to the umbilicus, which was thought to be attached to the uterus. All clinical laboratory tests were essentially negative. A diagnosis of a huge fibroid uterus was considered and an exploratory laparotomy was performed. A huge cystic ovarian mass was found on the right side which filled the pelvis and displaced the uterus but which was not attached to any of the adjacent pelvic structures. A supracervical hysterectomy and bilateral salpingo-oophorectomy were performed. The patient made an uneventful recovery and has remained well for over 3 years.

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*Gross Description.*—The uterus, left Fallopian tube, and the left ovary were not grossly remarkable. The right Fallopian tube, which was greatly elongated, measured 17 cm. in length and was flattened over the dorsum of a huge cystic mass occupying the site of the right ovary. This measured 22 by 21 by 12 cm. and was everywhere intact, with a smooth pearly white serosal surface. On section it was found to be unilocular and was

Fig. 1.

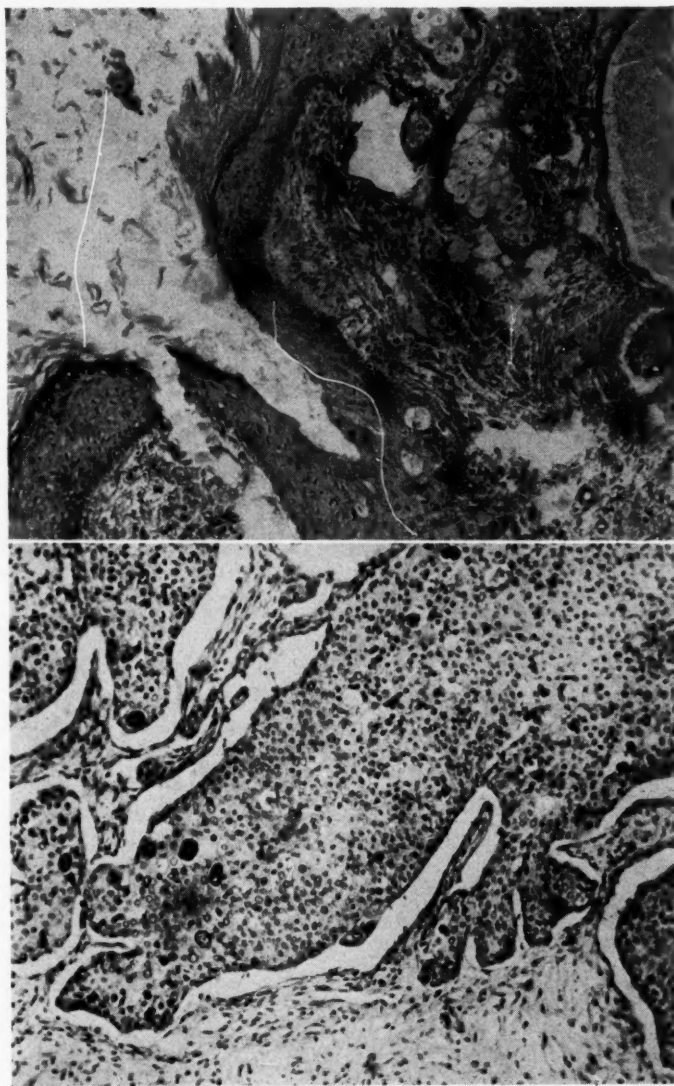


Fig. 2.

Fig. 1 (Case 1).—Shows the epidermal lining of the cystic teratoma with an underlying sebaceous gland. ( $\times 100$ .)

Fig. 2 (Case 1).—Shows the infiltrating nests of neoplastic squamous cells. ( $\times 100$ .)

filled with turbid brown fluid. Most of the wall averaged only 0.1 to 0.3 cm. in thickness and had a smooth inner lining. A few hairs projected from a granular, yellow-white, friable excrescence. One portion of the wall was greatly thickened up to 2 cm. and had a roughened granular lining. It was composed of firm gray-white tumor tissue.

*Microscopic Description.*—Sections from the thin-walled portion of the cystic tumor revealed the lumen to be lined by typical stratified squamous epidermis, beneath which some hair follicles and sebaceous glands were present. In other sections the lining epidermis was completely desquamated and a foreign body granulomatous reaction was seen in the denuded lining. Sections from the thickened portion of the tumor revealed numerous nests and masses of neoplastic squamous cells infiltrating an abundant amount of fibrous stroma. The large polyhedral tumor cells contained abundant pink cytoplasm and had well-defined intercellular bridges. Most of the rather large hyperchromatic nuclei varied only moderately in size and shape, but a few huge black bizarre forms were also seen. Moderate numbers of both typical and atypical mitoses were present. Numerous individual dyskeratotic cells were seen, but no keratin pearls were found. The neoplasm was everywhere viable with no foci of necrosis.

*Diagnosis.*—Squamous-cell carcinoma arising in benign cystic teratoma of the right ovary.

CASE 2.—Mrs. E. S., an 88-year-old white woman, was admitted to the Herrick Memorial Hospital, Berkeley, Calif., on Aug. 9, 1950, complaining of weakness and abdominal pain for the past two days. For the past two years she had developed abdominal swelling which was accompanied by increasing ankle edema. This had become quite severe about three months ago, at which time she was bedridden. The edema was relieved by diuretics and digitalization, and she had since remained under fairly good control until the day prior to admission. At this time she developed moderate abdominal pain which gradually increased in intensity. Physical examination revealed an elderly emaciated white woman who appeared chronically ill. Pertinent findings included a somewhat enlarged heart and an irregular rhythm, but no murmurs were heard. The abdomen was swollen with bulging flanks, shifting dullness, and a positive fluid wave. A somewhat rounded tumor mass arising from the left side of the pelvis was palpable in the hypogastrium. Laboratory work consisted only of an urinalysis which was essentially negative. The patient's condition deteriorated rapidly and she died on Aug. 10, 1950, one day after admission.

*Gross Autopsy Findings.*—Only the pertinent autopsy findings will be given. The peritoneal cavity contained 1,500 c.c. of cloudy yellow fluid. The serosal surface was hyperemic throughout and was covered by granular to shaggy yellow-gray material. A large tumor mass measuring 19 by 18 by 10 cm. was found occupying the site of the left ovary. Both the distal ileum and the sigmoid colon were firmly adherent to it and could not be dissected free. The external surface of the tumor was smooth and pearly white except where it was adherent to the bowel. On section the bulk of the mass was composed of a unilocular cyst with an extremely thin wall averaging only 0.1 to 0.3 cm. in thickness. The lumen contained a thin amber fluid with numerous floating fat droplets, as well as a large dark brown hair ball measuring 8 cm. in diameter. The inner lining was smooth in some places and roughened and granular in others. The wall in one portion of the cystic tumor consisted of a large solid mass of tumor tissue measuring 7 cm. in maximal diameter and 3 cm. in thickness. This was firm and gray white with numerous soft friable yellow zones. The tumor had infiltrated the outer wall of the adherent sigmoid colon, but the mucosal lining was nonetheless everywhere intact. The terminal ileum was also infiltrated, but the wall was extremely friable and the lining mucosa was eroded and granular in many places.

*Microscopic Description.*—Sections from the thin-walled portion of the cystic tumor revealed the lumen to be lined by typical stratified squamous epidermis, beneath which hair follicles and sebaceous glands were present. In other sections the epidermal lining was desquamated, and there was an intense foreign-body granulomatous reaction in the denuded lining. Sections from the solid portion of the tumor revealed numerous irregular nests and masses of neoplastic squamous cells infiltrating an abundant amount of fibrous stroma. Some of the well-differentiated epithelial masses contained large keratin pearls and were composed of large polyhedral cells with abundant cytoplasm and well-defined intercellular bridges. Other more anaplastic epithelial masses were composed of small immature cells containing little cytoplasm and exhibiting rather marked nuclear pleomorphism. These contained numerous



mitoses but no keratin pearls. Extensive areas of necrosis were present, some of which were replaced by highly vascular granulation tissue. Sections of the colon revealed the outer wall to be infiltrated by the neoplasm as far as the submucosa, but the intact mucosa was not involved. A pronounced degree of melanositis coli was present. Sections of the ileum revealed

Fig. 3.

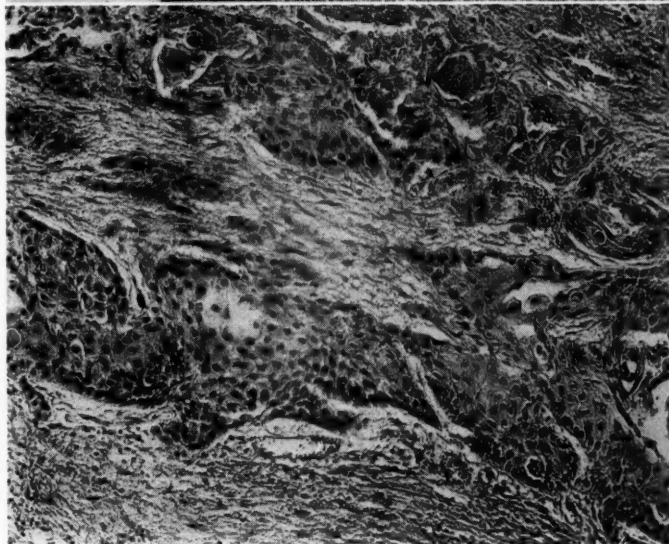
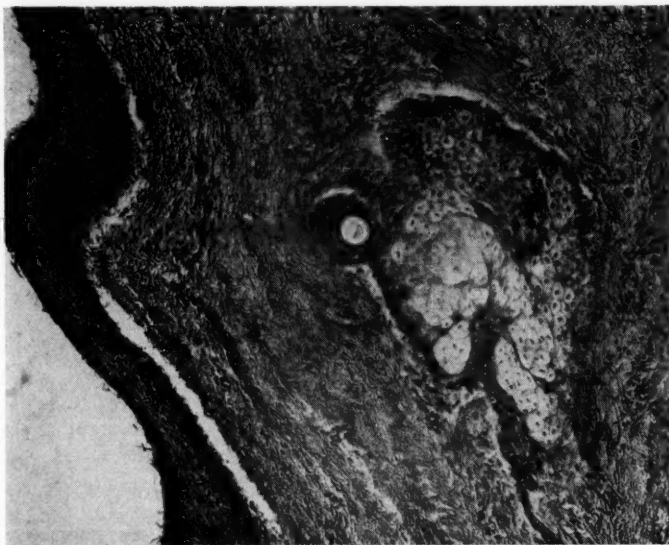


Fig. 4.

Fig. 3 (Case 2).—Shows the epidermal lining of the cystic teratoma with an underlying sebaceous gland. ( $\times 100$ .)

Fig. 4 (Case 2).—Shows the infiltrating nests of neoplastic squamous cells. ( $\times 100$ .)

extensive neoplastic infiltration of the entire wall, much of which was necrotic. The serosal surface exhibited an intense acute inflammatory process and was covered by abundant fibrino-purulent exudate.

*Diagnoses.*—1. Squamous-cell carcinoma arising in benign cystic teratoma of the left ovary.

2. Carcinomatous infiltration of sigmoid colon and terminal ileum, with necrosis and perforation of ileum.
3. Acute fibrinopurulent peritonitis.

Fig. 5.

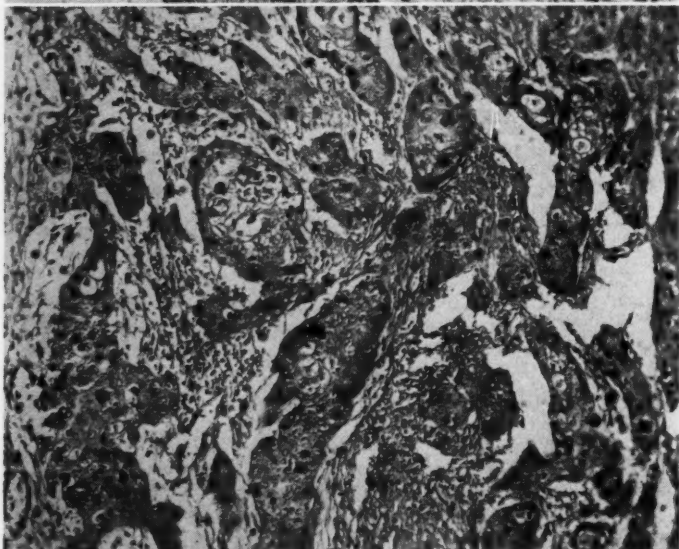
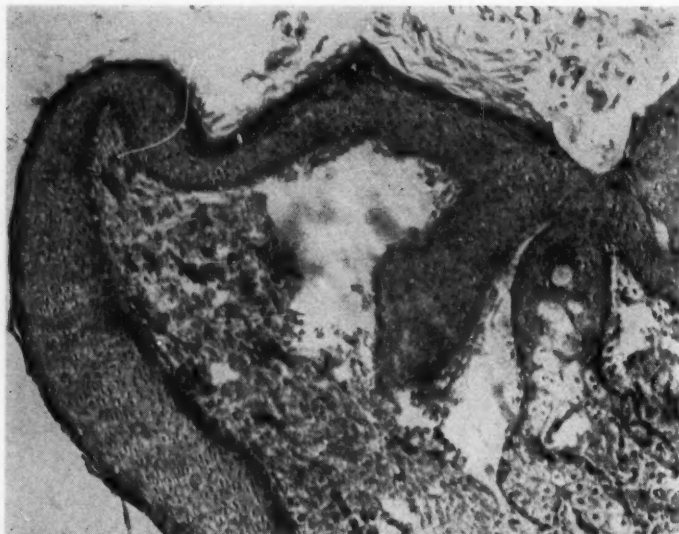


Fig. 6.

Fig. 5 (Case 3).—Shows the epidermal lining of the cystic teratoma with an underlying sebaceous gland. ( $\times 100$ .)

Fig. 6 (Case 3).—Shows the infiltrating nests of neoplastic squamous cells. ( $\times 100$ .)

CASE 3.—Miss M. K., a 26-year-old white woman, entered the Mercy Hospital, San Diego, Calif., on Feb. 13, 1951, because of vaginal discharge and pain in the left lower quadrant of the abdomen. For the past five weeks a considerable amount of fluid had been draining from the vagina. An examination two weeks prior to admission had revealed a palpable nodular mass arising from the left side of the pelvis and extending up to the umbilicus, a portion of which was felt in the cul-de-sac on rectal examination. Vaginal examination re-

vealed a small uterus which was displaced to the right. In addition a ragged fistulous orifice in the left fornix was found, from which a biopsy was taken. Histological examination revealed only acellular necrotic tissue. Physical examination on admission revealed a thin white woman who weighed only 104 pounds. No significant abnormalities of the head, neck, lungs, and heart were found. Abdominal, vaginal, and rectal examination confirmed the previous findings. Urinalysis and blood count revealed no significant abnormalities. An exploratory laparotomy was performed on Feb. 14, 1951. The left ovary was replaced by a multilocular cyst measuring approximately 25 by 12 by 10 cm., a portion of which was present in the cul-de-sac. It was adherent to the posterior surface of the uterus and upper vagina, and appeared to communicate with the fistulous orifice in the left vaginal fornix. During the course of a difficult removal the cystic tumor was ruptured with escape of hair, cheesy material, and large chunks of tumor tissue. A frozen section was performed and a diagnosis of carcinoma was made. A panhysterectomy and bilateral salpingo-oophorectomy was performed but it was felt that not all of the tumor had been successfully removed from the pelvis. The patient made an uneventful recovery with no complications and was discharged from the hospital seven days later. She subsequently developed generalized abdominal carcinomatosis and died four months later.

*Gross Description.*—The specimen consisted of an oval cystic tumor weighing 170 grams. Most of the surface was smooth and pearly white, but a portion was composed of shaggy friable tissue. Section revealed a lumen measuring 7 cm. in maximal size which was filled with cheesy material. The thin-walled portion of the tumor had a smooth lining with projecting hairs in some areas and a granular reddened lining in others. The greatly thickened portion of the wall was composed of firm gray-white tumor tissue in which numerous friable yellow areas were present. Approximately 15 Gm. of friable tumor tissue was received in separate pieces. The uterus, cervix, Fallopian tubes, and right ovary were also received. The posteroinferior surface of the small symmetrical uterus was rough and shaggy. Sections revealed friable yellow-gray tumor tissue infiltrating the outer myometrium as well as the outer portion of the posterior cervix. The opened endometrial cavity had a thin, smooth, tan lining. The small oval external os was surrounded by a generous cuff of portio and the endocervical canal was patent and free from gross change. The elongated left Fallopian tube was swollen and edematous. The right Fallopian tube and ovary were free from significant gross change.

*Microscopic Description.*—Sections from the thin-walled portion of the cystic tumor revealed an epidermal lining of typical stratified squamous type, beneath which sebaceous glands and hair follicles were present. In other sections the epidermal lining was desquamated and a foreign-body granulomatous reaction was seen in the denuded lining. Other sections from the thickened portion of the wall revealed irregular infiltrating nests of neoplastic squamous cells, which were rather anaplastic. The large irregular nuclei were hyperchromatic and varied considerably in size and shape. Numerous mitoses of both typical and atypical type were scattered throughout. No keratin pearls were present, and only a few scattered individual dyskeratotic cells were found. Large portions of the neoplasm were necrotic. Sections from the uterus revealed the outer myometrium to be infiltrated by nests of neoplastic squamous cells, much of which material was necrotic. Sections of the cervix revealed the portio to be lined by typical stratified squamous mucosa and the endocervical canal by tall columnar epithelium, with no evidence of neoplastic transformation.

*Diagnoses.*—1. Squamous-cell carcinoma arising in benign cystic teratoma of the left ovary.

2. Carcinomatous infiltration of the uterus, cervix, and upper vagina.

### Comment

The incidence of squamous-cell carcinoma arising from the epidermal lining of a benign cystic teratoma of the ovary is rather small. The most reliable statistics are those of the Mayo Clinic because of the rather large num-

ber of cases involved. Combining their own material with that previously reported by Masson and Ochsenhirt, Counseller and Wellbrock state that there were 7 such cases in a total of 408 cystic teratomas surgically removed between 1912 and 1931, for an incidence of 1.7 per cent.<sup>5</sup> Kent's 4 cases were present in a series of 50 cystic teratomas for an apparent incidence of 8 per cent.<sup>6</sup> In view of the rather small total number of cases involved, I consider this to be an excessively high figure. If all subsequent cases of benign cystic teratoma at this institution prior to the occurrence of a fifth case were included in the calculations the incidence would undoubtedly be considerably lower than that quoted by this author.

The age of the patient was not mentioned in three of the cases reported in the literature. The average age in the other 60 cases at the time of diagnosis was 49 years. Between the ages of 20 and 29 years there were 5 cases, or 8 per cent; between 30 and 39 years 6 cases, or 10 per cent; between 40 and 49 years 21 cases, or 35 per cent; between 50 and 59 years 13 cases, or 22 per cent; and between 60 and 69 years 13 cases, or 22 per cent. The two extremes are Caillot and Boulez' second case of a 19-year-old girl which was reviewed by Bowles,<sup>7</sup> and my second case of an 88-year-old woman. Hence approximately 80 per cent of the cases occurred between the ages of 40 to 70 years, with the greatest incidence during the fifth decade. Prior to this time the two oldest patients on record were Bowles' own case and one of Denis' which he had reviewed, both of whom were 68 years of age.

Of the 48 cases in which the information was given the left ovary was involved in 29 cases, or 60 per cent, and the right in 19, or 40 per cent. Despite a seemingly higher incidence in the left ovary I do not consider these figures to be statistically significant in view of the lack of specific information in the other 25 cases and the relatively small number of cases from which these percentages are derived. Two cases are of interest because of the presence of bilateral cystic teratomas, one of which contained a squamous-cell carcinoma. One was a case of Krukenberg's which was reviewed by Masson and Ochsenhirt,<sup>1</sup> and the second was Bowles' personal case. Although no case of bilateral cystic teratomas with squamous-cell carcinoma arising in both of them has yet been reported, there is no reason why such an occurrence is not theoretically possible.

Unfortunately from the standpoint of clinical diagnosis the symptoms are nonspecific in character. Of the 49 cases in which there was adequate clinical information the two most common manifestations were (1) palpable lower abdominal tumor and (2) lower abdominal pain. Both abdominal tumor and pain were present in 25, or approximately 50 per cent, of the cases, abdominal tumor alone in 12, or approximately 25 per cent, and abdominal pain alone in 12, or approximately 25 per cent. Other symptoms mentioned were those resulting from increased intrapelvic pressure, namely increased frequency of urination, constipation, a sense of pelvic heaviness, and low backache. Consequently, although the presence of an ovarian cystic mass was suspected in the majority of cases, rarely was the possibility of a malignancy suspected prior to or occasionally even after surgery. As a result Cardwell



and Pund<sup>9</sup> strongly emphasized that, since the development of a malignancy in a cystic teratoma of the ovary cannot be definitely determined preoperatively, all such tumors should be removed without delay when the patient's general condition will permit. In 5 of the 49 cases the abdominal tumor was known to have been present for a period of 8, 13, 16, 19, and 20 years, respectively. Had the cystic teratomas in these cases been removed when first noticed, opportunity for the development of a squamous-cell carcinoma would no longer have existed. Two of these women are known to have died of their malignancy while the fate of the other three is not known.

Since the definitive diagnosis is invariably established by the pathologist, all cystic teratomas of the ovary once removed should be carefully examined. This important point is well exemplified by the case reported by Williams and Bloom<sup>13</sup> in 1942. Spontaneous rupture of a large dermoid cyst of the ovary had occurred in a 40-year-old woman, for which an oophorectomy was performed. The original pathological report consisted of a gross diagnosis of "simple dermoid cyst," and no microscopic examination was performed. Nine months later the patient returned with a large mass in the cul-de-sac which was adherent to both the uterus and rectum. Since it was considered to be nonresectable only a biopsy was taken which was reported as "squamous cell (epidermoid) carcinoma." The original specimen was apparently discarded and hence was not available for further study and review at the time of the second operation. The patient died about 5 months after surgery.

The only known treatment at the present time which offers the patient any hope is surgery. The most important factors at the time of surgery which determine the probable outlook for the patient are (1) rupture and (2) adherence to adjacent pelvic structures, according to Counseller and Wellbrock.<sup>5</sup> The case of Williams and Bloom is an excellent example of the first factor, and my second and third cases of the second factor. Death in the second occurred as a result of peritonitis due to extensive necrosis and perforation of the infiltrated terminal ileum. In the third there was local extension to the uterus and vagina, with death occurring 4 months after surgery due to generalized abdominal carcinomatosis. The absence of these two phenomena in my first case has given the patient a potential opportunity for a complete cure of her malignancy.

The prognosis in these cases is an extremely grave one. Two of the known fatal cases were diagnosed only at the time of autopsy, one of which was Kent's<sup>6</sup> first case, and the other my second case. In the 26 patients known to have died of their malignancy following surgery, there was an average survival time of only 5 months with a range of 3 days to 14 months. Only 4 patients are known to have survived 5 years or longer. One of these, a case of Lapouge's reviewed by Masson and Ochsenhirt,<sup>1</sup> died of a recurrence after 7 years. The other 3 patients were reported as alive and well at 15 years by Counseller and Wellbrock,<sup>5</sup> 6 years by Fein and Hobart,<sup>8</sup> and 5 years by Masson and Ochsenhirt.<sup>1</sup> Four patients at the time of the reports were alive and well for periods ranging from 1 to 3 years in which the final outcome

is not known. The fate of the patients in the other 27 cases was not stated by the various authors. Of these 8 were known to have extension to adjacent pelvic structures at the time of surgery and hence could not be expected to have survived for any great length of time. Considering only the 32 patients known either to have died of their malignancy or to have survived 5 years or longer, there is a mortality rate of 87.5 per cent at the end of a 5 year period of time.

### Conclusions

1. Sixty acceptable cases of primary squamous-cell carcinoma arising in benign cystic teratomas of the ovary are found on review of the literature and 3 additional cases are reported in detail.

2. The first case is that of a 40-year-old woman who has survived for a period of over 3 years following surgery and diagnosis. The second is that of an 88-year-old woman who is now the oldest patient on record. Death was due to peritonitis as a result of carcinomatous infiltration of the terminal ileum with extensive necrosis and leakage of the bowel wall. The third is that of a 26-year-old woman who had local pelvic extension to the uterus and vagina. Death occurred 4 months after surgery due to generalized abdominal carcinomatosis.

3. The incidence of squamous-cell carcinoma in benign cystic teratomas is approximately 1.7 per cent.

4. The average age at the time of diagnosis is 49 years. Approximately 80 per cent of the cases occur between the ages of 40 to 70 years, and the greatest incidence, 35 per cent, occurs during the fifth decade.

5. The diagnosis of a malignancy developing in a cystic teratoma of the ovary is rarely made clinically and hence surgical removal of all clinically suspected cystic teratomas is imperative, if the patient's clinical condition permits. Small though it be, a 1.7 per cent incidence is in itself adequate justification for oophorectomy from a prophylactic viewpoint, even if one were to ignore all the other complications to which benign cystic teratomas are subject.

6. All cystic teratomas of the ovary require careful gross and microscopic study to rule out the presence of a previously unsuspected squamous-cell carcinoma.

7. In the absence of existing distant metastases at the time of surgery, the two most important factors determining the probable outcome in the individual case are the presence or absence of (1) rupture and (2) adherence to adjacent pelvic structures.

8. Only 4 of the 63 patients are known to have survived for a period of 5 years or longer, and of these one died of recurrence 7 years after surgery.

9. In the 32 cases the outcome of which is known there is a 5 year mortality rate of 87.5 per cent, with an average survival time of only 5 months following surgery.

I wish to express my appreciation to Dr. Lester S. King of the Illinois Masonic Hospital, Chicago, Ill., for permission to use the first case, to Dr. Hamilton R. Fishback of the Herrick Memorial Hospital, Berkeley, Calif., for the second case, and to Drs. Ralph L. Hoffman and Dominic A. De Santo of the Mercy Hospital, San Diego, Calif., for the third case.

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## HYPERESTRINISM IN OLD WOMEN

### Report of a Case With Cortical and Medullary Hyperplasia of the Ovaries and Possible Adrenal Hyperactivity

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POSTMENOPAUSAL hyperestrinism may manifest itself as bleeding from an actively hyperplastic endometrium, tender swelling of the breasts, or a pronounced rise in the number of cornified epithelial cells in the vaginal smear. The presence of carcinoma of the endometrium may likewise point to an excess of estrogens. The principal evidence in favor of this is: (1) the relatively high incidence of endometrial carcinoma in known hyperestrogenic states,<sup>1, 2</sup> (2) the common accompaniment of endometrial carcinoma by an elevation in cornified cell count in the vaginal smear,<sup>3, 4</sup> and (3) the often-observed successive chronological sequence of endometrial hyperplasia, polyps, and carcinoma.<sup>5</sup>

In certain instances of postmenopausal hyperestrinism, the pathogenesis is clear, either an overproduction of estrogens by an ovarian tumor or a decreased inactivation of them due to liver disease. In cases other than these, however, the etiology has remained an enigma. The approach to the problem so far has been twofold: (1) investigation of hepatic inactivation of estrogens, and (2) pathological study of the ovaries.

Biskind and Biskind<sup>6</sup> have shown that in female rats the liver loses its ability to inactivate estrogens if the diet is deficient in vitamin B complex. Ayre,<sup>4</sup> following this lead, reported that of twenty women with cancer of the uterus 90 per cent showed evidence of hyperestrinism in their vaginal smears coupled with low urinary excretion levels of thiamine.

Woll and his co-workers<sup>7</sup> investigated the pathology of the ovaries in endometrial carcinoma in an attempt to find a morphological basis for estrogen overproduction. They discovered a number of lesions that were significantly more frequent in endometrial carcinoma ovaries than in controls. Most commonly encountered was hyperplasia of the cortical stroma which was twice as frequent in the controls. A relatively uncommon finding, "thecomatosis" or "luteinization" of the cortical stroma (in which nests of large polyhedral cells resembling corpus luteum cells make their appearance) was four times as frequent; while "cortical granulomas" (tubercle-sized foci of epithelioid cells, Langhans giant cells, and lymphocytes) were seven times as frequent.

Shaw and Dastur,<sup>8</sup> concentrating on the ovarian hilus, described therein nests of large cells in over 50 per cent of cases of endometrial and endocervical cancer; they were unable to find these cells in control ovaries. The work of these authors has been criticized because although their cells bear a striking



resemblance to the androgen-producing hilus (Leydig) cells described by Berger,<sup>9</sup> Sternberg,<sup>10</sup> and others, no mention was made of this resemblance. Husslein<sup>11</sup> has reported four cases of postmenopausal cystic hyperplasia of the endometrium associated with hyperplasia or small tumors of the hilus cells. One of these tumors was 0.3 cm. in diameter; the size of the other was not stated.

Hilus-cell hyperplasia may go hand in hand with luteinization of the cortical stroma in postmenopausal hyperestrinism. A single case report by Simard and Simard<sup>12</sup> was that of a 67-year-old woman who complained of postmenopausal bleeding and painful swelling of the breasts with secretion. Following bilateral oophorectomy and hysterectomy there were regression of symptoms and the onset of hot flashes. The ovaries showed luteinization of the cortical stroma\* as well as marked hilus-cell hyperplasia.

The adrenal cortex, though a known estrogen producer, has received little attention regarding its possible role in postmenopausal hyperestrinism, as this gland is rarely made available to the pathologist in such cases. One fragment of evidence showing that the adrenal cortex may play a role is the example cited by Novak<sup>13</sup> of a woman with endometrial hyperplasia fourteen years after bilateral oophorectomy.

The case to be presented is one of an elderly woman with carcinoma of the endometrium and excessive cornification in the vaginal smear. The ovaries showed cortical stromal hyperplasia with luteinization, medullary hyperplasia with focal hilus-cell production on one side, and a nodule of atypical hyperplastic hilus cells on the other. The persistence of excessive cornification of the vaginal smear following hysterectomy and oophorectomy suggested that the adrenal cortex may have been contributing to the hyperestrinism.

### Case Report

A. M. (M.G.H. Hosp. 497740). A 73-year-old white mother of one was admitted because of profuse vaginal bleeding of several hours' duration. There had been no bleeding since the menopause when the patient was 45 years old, until two years before entry, when she stained on several occasions and then stopped. Physical examination showed moderate facial hirsutism. The cervix was dilated and blood was flowing from it. Vaginal smear cell counts showed 76 per cent cornified cells. A dilatation and curettage specimen showed adenocarcinoma; 3,600 mg. hours of radium were placed in the endometrial canal. Six weeks later a total hysterectomy and bilateral salpingo-oophorectomy were performed. Two-year follow-up showed no recurrence of tumor; the hirsutism was stated to be still present. Vaginal smear cell counts three months and two years postoperatively showed 56 and 72 per cent cornified cells, respectively.

Pathological examination (37-1818) disclosed a uterus which measured 6.5 by 4.5 by 4.0 cm.; the myometrium was 1.4 cm. in thickness. In the left cornu on the endometrial aspect of the posterior wall was a fungating mass 2 cm. in diameter. Microscopic study revealed an adenocarcinoma Grade 2 of the endometrium without invasion of the myometrium. The remaining endometrium was thin; its surface was lined by simple flat to columnar epithelium; its stroma was composed of spindle cells, an abundance of thin collagen fibrils, and moderate numbers of lymphocytes and plasma cells. The scattered glands varied in size and shape and were lined for the most part by pseudostratified columnar epithelium; an occasional gland had the morphology of carcinoma *in situ*.<sup>5</sup> The myometrium was com-

\*This was not diagnosed as such, but it is clearly present, judging from the microscopic description and the published photomicrographs.

posed of bundles of large muscle fibers resembling those encountered in uteri of the reproductive age group; its blood vessel walls were considerably thinner than those characteristic of the senile uterus. The tube which was examined microscopically showed a well-developed muscle layer; its villi had fibrous cores; in certain areas it was lined by tall epithelium, many of whose cells were ciliated and some of which had the appearance of plump secretory cells.

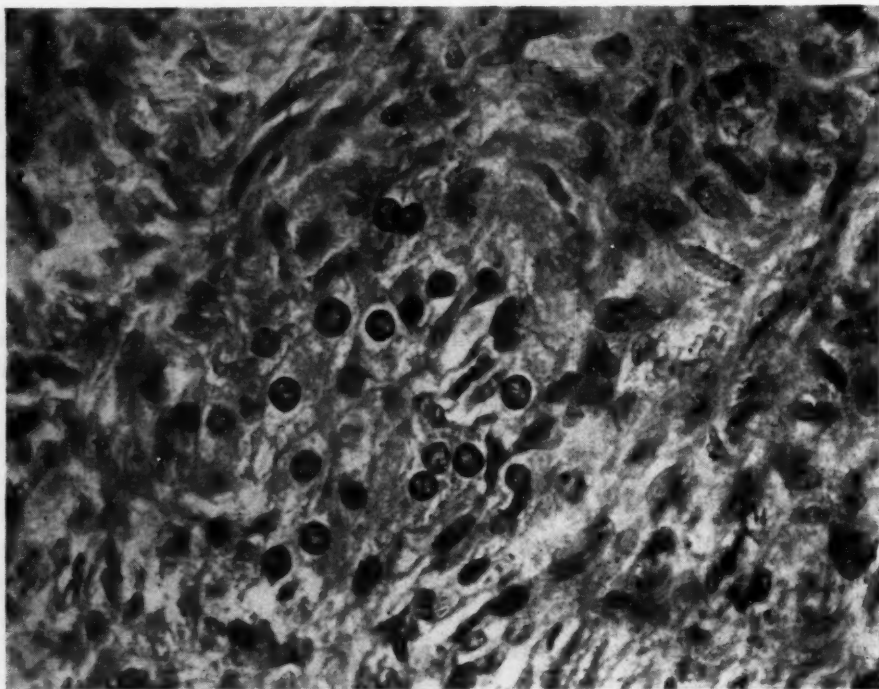


Fig. 1.—Nest of polyhedral luteinized cells with round nuclei lying in a stroma characterized by plump oval nuclei.

The right ovary measured 3.0 by 3.0 by 2.0 cm.; the left, 2.0 by 1.5 by 1.0 cm. One microscopic section of each ovary, stained with phloxine methylene blue, was available for study. The right ovary presented a stringlike adhesion of loose collagenous tissue on its cortical surface. The cortical stroma was abundant and dipped irregularly into the medulla at several points. It was composed of intersecting fascicles and whorls of wavy delicate collagen fibers. The stromal cells were generally characterized by small oval and spindle nuclei; in some regions, however, they were considerably larger, plump, and densely packed. Throughout the cortical stroma were unusual structures of two types. (1) Disseminated in nests (up to several hundred cells in one plane of section) were large polyhedral cells characterized by eosinophilic, occasionally foamy cytoplasm, and round, glassy nuclei with single nucleoli (Fig. 1); these cells resembled luteinized theca cells. (2) Irregularly distributed were gently lobulated, pale gray scars which were quite uneven in shape and size, varying up to 8 mm. in longest dimension. These scars, unlike the numerous corpora albicantia and fibrosa which were present in the central portion of the ovary, had little affinity for eosin. Within the scars were scattered stromal cells and delicate capillaries in varying numbers. Transitional forms between (1) and (2) were frequently observed; these were scars containing ill-defined zones of diffusely arranged luteinized cells (Figs. 2 and 3).

In the medulla of the right ovary was a sharply circumscribed, irregularly outlined, pale, basophilic nodule, measuring 0.6 to 0.7 cm. in longest dimension (Fig. 4); at its cortical border it interdigitated with prolongations of the cortical stroma and abutted against corpora albicantia; along its hilar border it extended irregularly between thick-

Fig. 2.

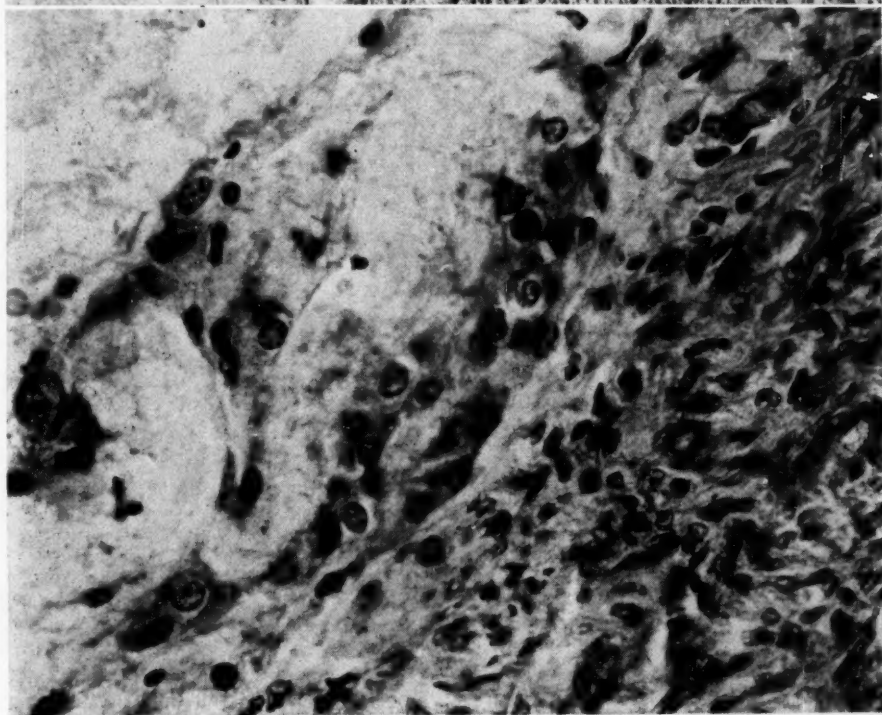
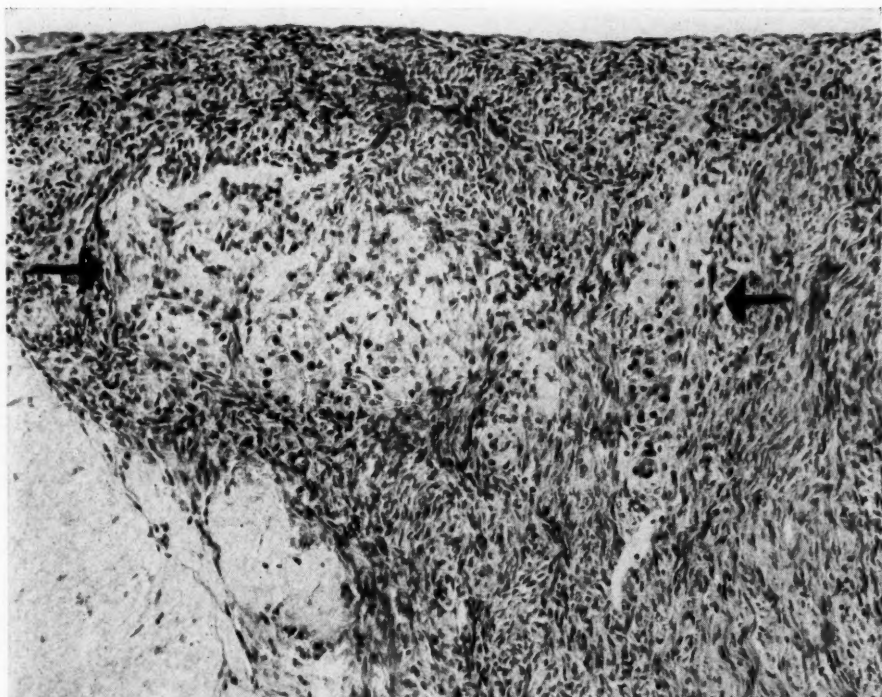


Fig. 3.

Fig. 2.—Irregular lesions (arrows) composed partially of luteinized cells and partially of scar tissue. A portion of corpus albicans is present in the left lower quadrant.

Fig. 3.—High-power view of scar containing luteinized cells (left upper portion of picture).



Fig. 4.

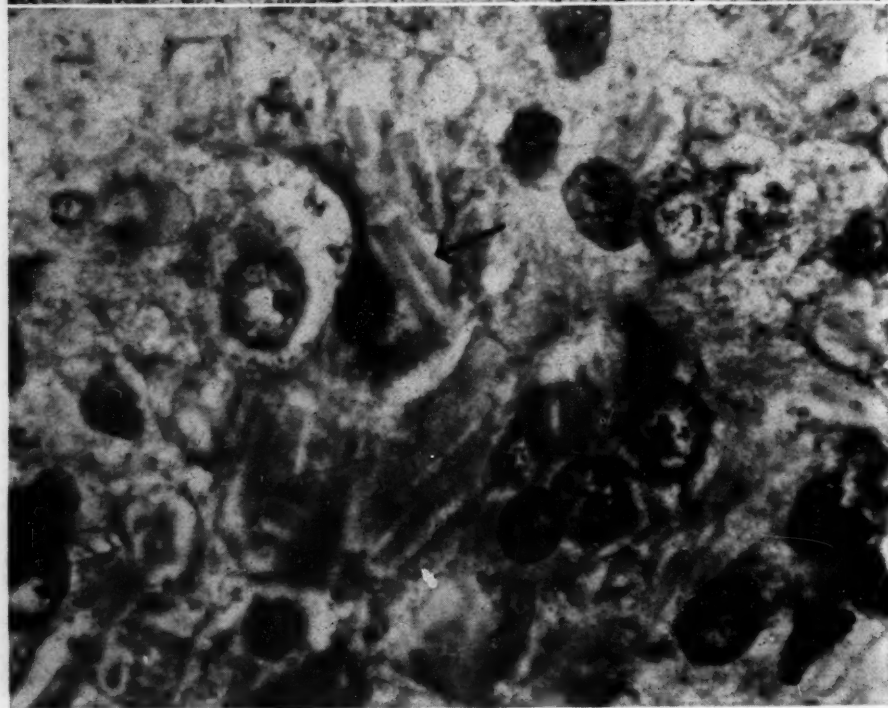
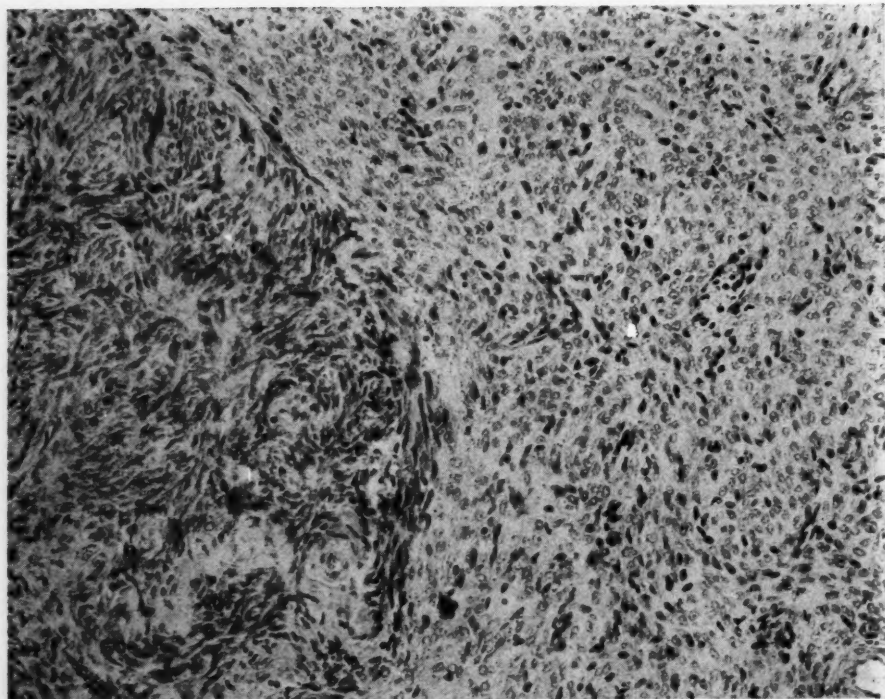


Fig. 5.

Fig. 4.—Nodule of medullary hyperplasia (right) adjacent to hyperplastic cortical stroma (darker tissue on left).

Fig. 5.—Crystalloids of Reinke (example at arrow).



Fig. 6.

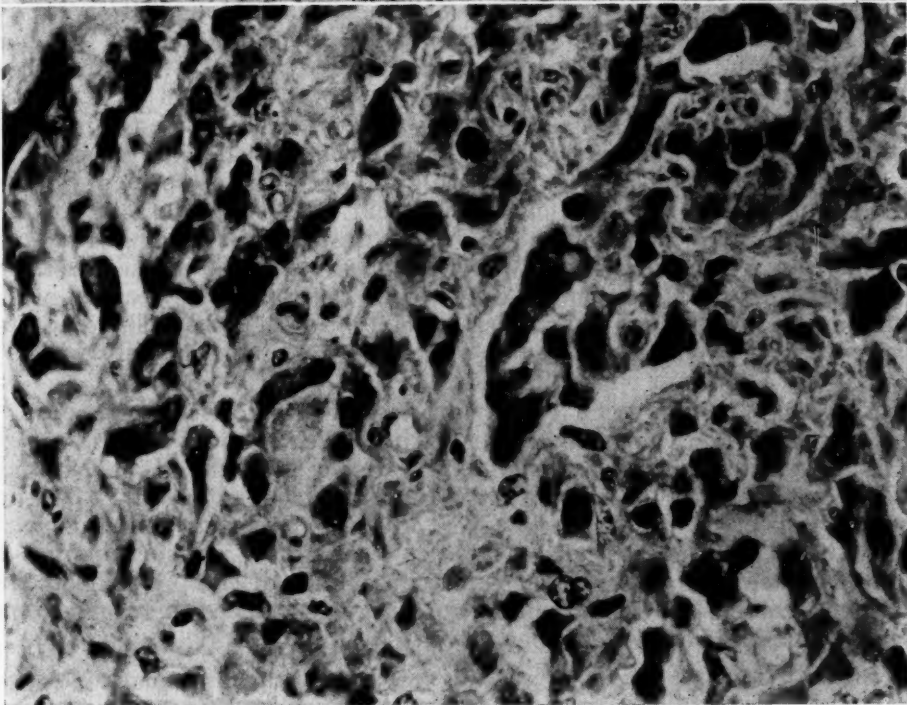
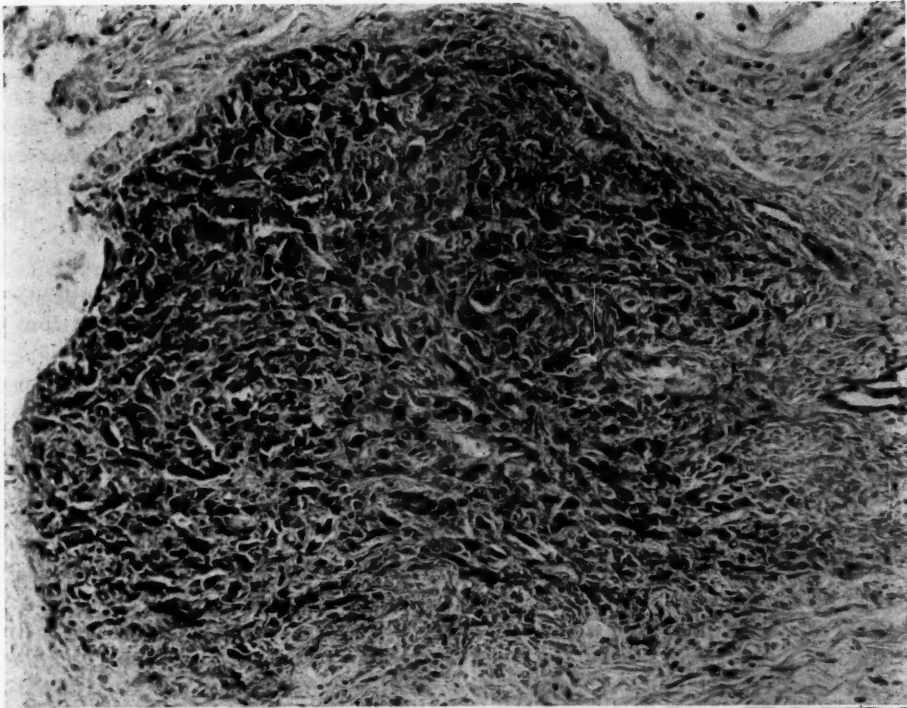


Fig. 7.

Fig. 6.—Atypical Leydig (hilus) cell nodule in hilus of left ovary.

Fig. 7.—High-power view of hilus cells in left ovarian nodule. Note shrunken character, bizarre shapes, and pyknotic nuclei.

walled blood vessels. This nodule was composed largely of uniform cells characterized by nuclei which were diffuse without fascicular or whorl arrangement; they were less closely packed and considerably larger and more oval than the cortical stromal nuclei. Between the nuclei was pale-staining homogeneous material which seemed to contain little in the way of collagen. Scattered especially within the periphery of the nodule were several nests of polyhedral cells numbering up to approximately 75 per nest (in a single plane of section). These cells were indistinguishable from the luteinized cells of the cortex except for the presence in their cytoplasm of numerous eosinophilic rods, so-called crystalloids of Reinke (Fig. 5). Within the nodule were also several small irregular foci of hyalinization. In the medulla elsewhere were a few small nodules of hilus cells.

The left ovary, although smaller, was essentially similar to the right in the histology of its cortex. In the medulla, however, there was no similar nodule of hyperplasia; the hilus-cell element was here represented almost entirely by a single triangular 2 mm. mass of cells close to the rete ovarii (Fig. 6). These cells were bizarre in shape, being rectangular, triangular, and oat-shaped; often their borders were indistinct and they appeared to anastomose with one another. The cytoplasm was densely eosinophilic; in it no crystalloids were identified; the nuclei were usually pyknotic; however, a few were pale with single nucleoli (Fig. 7). Between the cells was dense collagenous tissue showing a focal scattering of lymphocytes.

#### Comment on Case

This 73-year-old woman presented several manifestations of hyperestrinism; she had carcinoma of the endometrium and a cornified cell count in the vaginal smear indicative of marked estrogen effect. The myometrium, uterine vasculature, and tube presented morphological features more suggestive of the reproductive age than of senility. The endometrium uninvolved by tumor was not actively hyperplastic; however, its epithelial elements were more prominent than expected; it is not impossible that it had been previously hyperplastic and that its appearance was altered by radiation and chronic inflammation.

The ovaries showed hyperplasia of the cortical stroma with the production of luteinized cells indistinguishable in their morphological characteristics from cells which compose many steroid-secreting tumors. The presence of numerous scars interpreted as involuted nests of lutein cells suggests that the latter may have been even more abundant in the past. The medulla of the right ovary showed hyperplasia of indifferent-appearing cells whose nature was ascertainable only from the more differentiated cells, the crystalloid-containing hilus cells with which they were intimately associated. The medulla of the left ovary showed a large nodule of shrunken eosinophilic cells which had a morphology consistent with hilus cells.

In summary we have an elderly woman with evidence of abnormal estrogen secretion, and cells in the ovaries (luteinized stromal and hilus) which are the morphological image of actively secreting steroid cells. The obvious inference is that these cells were secreting the excess estrogens.\* The most surprising aspect of the case, however, was the persistence of the marked estrogen effect in the vaginal smear two years after oophorectomy. This suggests at once that, excluding the rare possibility of ectopic ovarian tissue, the adrenal cortex, the only remaining estrogen producer in the body, must also have been and remained hyperactive.

#### Discussion

The problem of evaluating the morphological changes that occur in the ovaries after the menopause is a difficult one. No statistical correlation with

\*There was also hirsutism, which may be evidence of excess androgen secretion. Facial hirsutism is not uncommon in elderly women; its pathological background has not been elucidated; it is possible in this case that either or both the luteinized stromal and hilus cells may have been producing androgens also.

endometrial hyperplasia or cornified cell count in the vaginal smear has been published. Endometrial carcinoma, which seems to have a background of hyperestrinism in most cases, is not the best criterion for excess estrogen, since the latter does not appear to be invariably associated, and other carcinogenic factors undoubtedly play important roles. Nevertheless, the demonstration that cortical stromal hyperplasia, luteinization of the stroma, and cortical granulomas are statistically unusually common in cases of endometrial carcinoma does suggest that these lesions bear some relation to hyperestrinism. The exact nature of this relationship can be no more than speculative at the present time. Since what are known to be steroid hormone-secreting cells are characteristically rich in cytoplasm, evidence is somewhat against the idea that hyperplastic stromal cells are estrogen-producers. More plausible as estrogen-secretors are the luteinized stromal cells, which are the morphological counterpart of premenopausal theca lutein cells. It is possible that more thorough sectioning of the ovaries might disclose these cells in most, if not all, otherwise unexplained cases of postmenopausal hyperestrinism. The cortical granulomas, which have a statistical correlation with endometrial carcinoma, have been logically interpreted as representing a granulomatous response to catabolized steroid hormone.<sup>7</sup>

A cause-effect relationship of hilus (Leydig) cell hyperplasia to hyperestrinism has less in the way of physiological or statistical backing. There is definite evidence that Leydig cells in males may produce estrogens.<sup>14</sup> Husslein's<sup>11</sup> cases of hilus-cell hyperplasia and neoplasia accompanied by endometrial hyperplasia are suggestive of such a function in females. The findings of Shaw and Dastur,<sup>8</sup> even though these authors failed to relate their cells to hilus cells, have been neither confirmed nor denied with adequate statistical proof. Through the kindness of Mr. Shaw, we have been permitted to examine slides from one of his cases illustrating the cells found in the ovaries of uterine carcinoma. These cells were present in two large nodules; one was composed of typical hilus cells; the other, of distinctly altered hilus cells which had an appearance indistinguishable from those of the left ovarian nodule in our case.\* The latter morphology is similar to that occasionally encountered in the Leydig cells of the testis in the Klinefelter syndrome<sup>15</sup>; it also resembles the morphology described for hilus cells following the administration of chorionic gonadotrophin, a hormone which stimulates hyperplasia and probably secretion on the part of these cells.<sup>10</sup> Hence, the cells of Shaw and Dastur and of our case may represent stimulated hilus cells.

The coexistence of luteinized stromal-cell and hilus-cell hyperplasia in the case of Simard and Simard<sup>12</sup> and in our case, plus the additional evidence of adrenal hyperactivity in the latter, suggests stimulation of several end organs or end cells by a single agent; this most logically would be a gonadotrophic hormone of pituitary origin, perhaps the luteinizing or luteotrophic hormone. A primary hyperplasia of two ovarian cell types or of both ovarian and adrenal cell types would appear less likely.

\*We were unable to identify crystalloids in the cells of Mr. Shaw's slides; this, however, by no means excludes their hilus (Leydig) cell nature.

### Summary

1. Postmenopausal hyperestrinism may be associated morphologically with hyperplasia and production of new cells of endocrine type in the ovaries.
2. These cells, luteinized stromal cells and hilus (Leydig) cells, may be the manufacturers of estrogens in the postmenopausal ovary.
3. The lutein cell nests may involute with the formation of scars.
4. It is possible that the adrenal cortex can participate with the ovaries in the production of postmenopausal hyperestrinism, and that both glands are stimulated by the anterior pituitary in such cases.
5. A case has been presented in which endometrial carcinoma and a pronounced estrogen effect in the vaginal smear of a 73-year-old woman were associated with ovarian cortical and medullary hyperplasia, production of luteinized stromal and hilus cells, and possible adrenal hyperactivity.

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## HYPOPOTASSEMIA, AS ENCOUNTERED ON A GYNECOLOGY SERVICE

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THERE has been a great increase in the interest of the clinical role of potassium metabolism in disease<sup>1-3</sup> during the past five years. This interest has been stimulated by the available methods for measuring the concentration of this cation and the adaption of the flame photometer to quantitative assay of biological fluids.<sup>4</sup> Cases of disturbance of potassium metabolism may occur on any gynecology service, and the purpose of this paper is to present a brief review of the metabolism, mechanisms of deficit, signs and symptoms, and management of this condition, as well as to report two typical cases of hypopotassemia.

In a review of 150 cases of hypopotassemia by Martin and his co-workers<sup>5</sup> 87.4 per cent (131 of 150) were due to decreased potassium intake. Of the 131 patients, 90, or 60 per cent, were under nasogastric suction therapy and were receiving parenteral fluids which did not contain potassium. Of the 150 patients 9 (6 per cent) had accelerated loss of potassium from the body by way of the urinary or gastrointestinal tracts, by such means as fistulas or diarrhea. Of the 150 cases 10 (6.7 per cent) were the result of a rapid shift of potassium from extracellular fluid into cells under the influence of insulin used in the therapy of diabetic coma.

Almost every postoperative surgical patient is a candidate for some degree of potassium deficiency,<sup>6</sup> reduction or elimination of potassium intake through the gastrointestinal tract being the most common basis of such hypopotassemia. Evidence has been presented showing that regularly repeated intravenous infusions cause an increased renal excretion of potassium<sup>7, 8</sup>; this loss of potassium chiefly results from the maintained large daily urine output and decreased potassium intake. Potassium losses are likewise very large in dehydration states and when there is excess sodium in the body; when there is excessive sodium in the extracellular fluids the potassium is moved out of the cell along with the intracellular water, often being thus displaced and replaced within the cell by sodium.

In 1923 Whipple<sup>9</sup> described a syndrome characterized by anorexia, nausea, vomiting, asthenia, and arterial hypotension. It was encountered as a postoperative complication and was believed to be connected with pancreatic lesions. It was found that this condition did not respond to the infusion of physiological salt solutions, and, in view of our knowledge today, it must certainly

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have been the result of prolonged and uncorrected hypopotassemia. In 1937 Baker and Richardson were treating this condition at the Johns Hopkins Hospital by the oral administration of a mixture of electrolytes which included some potassium, and their results were good.<sup>10</sup>

### Metabolism of Potassium

Potassium is concerned in at least four fundamental physiological processes.<sup>11</sup> It acts, by local chemical (electrolyte) effect, in the maintenance of (1) normal water balance and distribution, (2) normal osmotic equilibrium, (3) normal acid-base equilibrium, and (4) normal muscle irritability.

Potassium is the chief cation of muscle cells and of most other cells, since it is present in the *intracellular* fluid. Sodium, on the other hand, is the chief cation of *extracellular* fluids of the body. Any considerable replacement of sodium by potassium in the extracellular fluids is accompanied by serious disturbances and may be fatal. No other cation can entirely replace potassium in the intracellular fluid without interfering to a definite extent with the functional activity of the cell. The exact mechanism whereby the proper distribution of sodium and potassium is maintained is not clearly understood. Peters and Van Slyke<sup>12</sup> state that potassium is prevented from diffusing out of the cells by a membrane or some other restraining factor present in the cellular or extracellular media. It also appears that the same or similar factors tend to prevent the undue passage of sodium into the cells under physiological conditions. In low concentrations, potassium is excitatory to cell function and in higher concentrations it is inhibitory. The effect of displacement of intracellular potassium by sodium on cell function is particularly important in relation to alterations of function of nerve synapses and myoneural junctions. In addition to this there is modification of the most fundamental properties of protoplasm and cells, including the permeability of cell membranes.

Potassium concentration of normal serum is 16 to 22 mg. per 100 c.c., averaging 19 mg. While there is little or no sodium in the erythrocytes, the average concentration of potassium in them is about 420 mg. per 100 c.c.

Absorption of potassium, under normal conditions, occurs almost solely from the gastrointestinal tract, but less than 10 per cent of potassium elimination occurs via the intestinal tract. Large quantities of it are so eliminated, however, in patients having diarrhea, but this excess may be due, in large part, to failure of reabsorption of digestive fluids rather than entirely to failure of absorption of the ingested salts. About 90 per cent of excreted potassium is eliminated in the urine.

### Mechanisms Productive of Potassium Deficiency

There are, as has been mentioned, two mechanisms which may cause loss of potassium from both the intra- and extracellular compartments of the body. These are (1) inadequate potassium intake, and (2) accelerated loss of potassium from the body. Inadequate intake occurs when the fluid intake is restricted and when only parenteral fluids which do not contain potassium are administered. Potassium deficits arise because the urine is never potassium

free, and as long as the individual continues to have an intake of water these ions continue to be lost although no potassium is being supplied.

As was stated before, loss of potassium from the body occurs through two major routes in health: (1) urine (90 per cent), and (2) stool (10 per cent). Excessive loss of potassium may result from increased excretion of potassium in the urine because of altered renal tubular function, in which there is impaired tubular reabsorption of potassium. Altered potassium excretion also occurs in any state associated with a *negative nitrogen balance*, of any etiology, since potassium then moves out of the cells with the nitrogen during normal tissue catabolism.

A deficit of extracellular potassium occurs when there are rapid shifts of potassium from the serum and interstitial fluid into the cells of the body; such shifts occur because of the effect of drugs or other substances which accelerate either carbohydrate or protein synthesis. Thus the administration of insulin, of large amounts of dextrose, and of testosterone cause a shift of potassium from the extracellular to the intracellular compartment. Any factor that results in hemodilution, such as administration of large volumes of parenteral fluid, will also cause a drop in serum potassium concentration.

### Symptoms and Signs of Potassium Deficit

The usual symptoms are general weakness, lassitude, diffuse atonicity of the intestinal tract with ileus, and cardiac irregularities, and hypotension. The severity of the symptoms and signs of potassium deficit are related to the serum potassium level. Decreased serum potassium affects neuromuscular physiology, the cardiac muscle, and the smooth muscle of the gastrointestinal tract.

All stages of change, from mere weakness to complete paralysis of the muscles of the trunk and extremities, may occur in the individual when the serum potassium level falls below 8 to 10 mg. per 100 c.c., or 2.05 to 2.56 meq. per liter.\*

Changes in conduction, irritability, and contractility of cardiac muscle occur when there are potassium levels under 10 to 12 mg. per 100 c.c. (2.56 to 3.07 meq. per liter). These changes are manifested by abnormalities in the electrocardiogram.

Clinically, the doctor may note systolic murmurs, gallop rhythms, cardiac dilatation, and hypotension. When potassium deficits are severe, cardiac arrest and death may occur. As was stated, lowered serum potassium may cause decreased tonicity and motility of the musculature of the gastrointestinal tract which results in adynamic ileus.

### Management

In the average postoperative case, when no suction removal of the stomach or small intestinal contents is employed, the patient loses approximately 1,000

\*A milliequivalent is the amount of an element or ion which will combine with or be equivalent in chemical combining power to 1/1000 of a gram atom of hydrogen. Milligrams are changed to milliequivalents by multiplying by the valence of the element or ion and dividing by the atomic or ionic weight. For example, a solution containing 31.1 mg. of potassium ion per liter contains 1 meq. per liter because the atomic weight of potassium is 31.1 and the valence is 1.

c.c. of body water through insensible loss, and 1,500 c.c. through urine output. The insensible loss may be replaced by parenteral glucose in water. To replace the electrolytes lost in the urine, 4 to 8 meq. of potassium per liter should be given in addition to 70 meq. of sodium per liter, and 50 meq. of calcium per liter.

An accurate intake and output record should always be maintained on any patient having continuous suction of the gastrointestinal tract. The amount of potassium to be replaced is dependent upon the amount calculated to be lost in the secretions so removed from the body.

When the average patient is having continuous nasogastric suction, she loses about 15 meq. of potassium per liter, 60 to 80 meq. of sodium per liter, and 120 meq. of chlorides per liter. In the case of small intestinal suction, the average patient loses 8 to 10 meq. of potassium per liter, 120 meq. of sodium per liter, and 80 to 100 meq. of chlorides per liter. Since the necessary amount of electrolyte replacement is dependent upon the amount of electrolyte lost, the above known averages can be referred to in roughly calculating the replacement.

In order to correct existing deficits of potassium, serum potassium values must be determined, in addition to which a clinical evaluation of the patient is essential. The amount of potassium to be given is dependent upon the combined findings. The patient should not receive more than 100 meq. of potassium parenterally in a twenty-four hour period, and should not receive more than 40 meq. of potassium per 1,000 c.c. of intravenous fluids. These should run in at the rate of not more than 20 drops per minute, lest the calculations be inaccurate and a state of hyperpotassemia be created. In hyperpotassemia the patient may exhibit paresthesias and myasthenic paralysis, although the greatest danger is cardiac arrest, which can occur at the serum level of 10 to 11 meq. per liter, or 39 to 43 meq. per 100 c.c.<sup>13</sup>

Three parenteral preparations of potassium chloride are used at the City of Detroit Receiving Hospital. A stock solution of 1.15 per cent potassium chloride is available. This contains 140 meq. per liter. Ampules containing 40 meq. of potassium chloride are available for dilution. In addition, Hartman's Lactate-Ringer's solution is available, which, when isotonic, contains 4 meq. potassium per liter.

If the patient is able to take oral therapy, potassium chloride tablets are available. One gram of oral potassium chloride contains 12.5 meq. of potassium. This method of administration is safe in that the body will not absorb more than it can handle and thus it will not lead to the development of hyperpotassemia.

### Case Reports

CASE 1.—D.R.H. 52-762, a 33-year-old, divorced Negro woman, was admitted to the City of Detroit Receiving Hospital on Jan. 16, 1952, with the chief complaint of lower abdominal pain and vaginal bleeding of six days' duration. Following the insertion of a catheter into the uterus for purposes of abortion on January 10, the patient experienced severe lower abdominal pain and vaginal bleeding. She became progressively weak and ill, suffered chills and fever, and reported to the emergency room on January 16. On examination, the patient appeared acutely ill, "toxic," and hyperpneic. The patient's temperature was 102° F., pulse 140, respirations 40. Her last menses had begun Sept. 15, 1951. The



abdomen was acutely tender, and there was rebound tenderness in the lower abdomen. Bowel sounds were present, but hypoactive. On pelvic examination a moderate purulent discharge was noted from the cervical os. On rectal examination, there was an enlarged, tender uterus, compatible with a 14 week intrauterine pregnancy. The parametrial areas on both sides were indurated and tender.

Shortly after admission the patient developed diffuse abdominal distention and ileus. Intestinal intubation was instituted immediately, as well as intensive antibiotic therapy. She received parenteral fluids including 1,000 c.c. of isotonic Hartman's Lactate-Ringer's solution daily. She responded to therapy, and on January 18 was able to take a liquid diet and this was gradually changed to a soft diet. By January 24 she had formed a pelvic abscess. Aspiration of the cul-de-sac on several occasions yielded large amounts of purulent material. Despite this she still maintained a febrile course. The abscess remained large, so a posterior colpotomy with drainage was done on January 30. Following this the patient again developed acute distention with ileus. Intestinal intubation was again instituted and she received parenteral fluids daily, which included 1,000 c.c. of isotonic Hartman's Lactate-Ringer's solution. The patient was not able to take fluids by mouth, so on Feb. 4, 1952, a serum potassium level was determined, revealing only 2.7 meq. per liter. Forty milliequivalents of potassium were then given daily parenterally. On Feb. 6, 1952, the serum potassium was 2.9 meq. per liter, while on Feb. 8, 1952, it was 4.0 meq. per liter. On February 8 the patient was able to take oral liquids and potassium chloride. On February 9 she was able to take a soft diet and thereby begin to receive adequate potassium intake through her food. She thereafter made an uneventful recovery and was discharged home on Feb. 24, 1952.

CASE 2.—D.R.H. 52-2944, a 52-year-old Negro woman, was admitted to the City of Detroit Receiving Hospital on March 2, 1952, in a stuporous state with a blood pressure of 76-56/52-0. Her hemoglobin was 10.5 Gm. She responded to parenteral fluids following which her blood pressure was 100/60.

Her menopause had occurred at the age of 45 but she had had intermittent vaginal bleeding from then until one year prior to admission, since which time she had had almost daily vaginal bleeding. Two weeks prior to admission she became confused and confined herself to bed. The patient's diet had been extremely scant and poor, containing little, if any, protein. There had also been an associated recent 30 to 40 pound weight loss.

The patient, on admission, was lethargic and showed evidences of dehydration. The abdomen was distended, but no muscle guarding, tenderness, or rigidity was present. Pelvic examination revealed carcinoma of the cervix, League of Nations Stage IV. Biopsy confirmed the impression, revealing squamous-cell carcinoma, histologic Grade III.

The patient received general supportive therapy, including parenteral fluids and isotonic Hartman's Lactate-Ringer's solution. Two days following admission she was able to eat, and was given a high protein, high caloric, and vitamin-rich diet. Serum potassium, on March 5, 1952, was 3.2 meq. per liter, and on March 7 was 4.1 meq. per liter. She responded well to general supportive therapy and was discharged on March 14, 1952, to the Radiology Clinic to begin deep x-ray therapy to the pelvis.

### Summary

Potassium metabolism, and the mechanisms of hypopotassemia, its symptoms and signs, and management are discussed. Two typical cases of "clinical" hypopotassemia on a gynecology service are presented. In the first case the hypopotassemia was due to inadequate intake of potassium while the patient was on continuous intestinal suction because of ileus associated with pelvic peritonitis. Accurate fluid intake and output records were maintained, but proper replacement, as outlined under Management, was not instituted

early enough. In the second case, the deficit was due to dehydration and inadequate oral potassium intake prior to admission. This was easily corrected with the intravenous administration of isotonic Hartman's Lactate-Ringer's solution and the taking of an adequate diet.

### Conclusions

1. "Clinical" hypopotassemia may be encountered on a gynecology service.
2. A basic understanding of the metabolism, mechanisms of deficit, symptoms, and signs is important in order to detect and treat this condition.
3. Accurate fluid intake and output records must be maintained, and proper potassium replacement must be accomplished. The intravenous replacement of potassium is not without danger and can be utilized only when carefully calculated margins of safety are allowed. The serum potassium determinations and volume of urine output constitute the main basis for calculation of the amount of potassium to be administered daily, and the oral route of replacement should be used whenever possible, including injection of a potassium solution through an in situ gastric or intestinal tube.

The author wishes to thank Dr. Charles S. Stevenson, Professor and Chairman of the Department of Obstetrics and Gynecology, Wayne University College of Medicine, for his encouragement, suggestions, and help.

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## DYSONTOGENETIC TUMORS OF THE FEMALE LOWER GENITAL TRACT\*

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**M**OST mesodermal tumors of the female lower genital tract are composed of mixed tumor types. However, there may be occasional failure to detect the tissue variation, since some of the constituents such as rhabdomyoblasts are frequently present in such minimal amounts. The selection of sarcoma or sarcoma botryoides as a title is, therefore, not entirely accurate. A comprehensive review of the subject was made by McFarland in 1935. He found these tumors under 119 different titles, mostly descriptive, such as myxoliposarcoma. To avoid the confusion as to whether these tumors are simple or mixed, he suggested the use of dysontogenetic tumors as a title. This refers to the histogenesis of the tumors and eliminates the descriptive nomenclature. Even with this broader term only 447 cases of the entire female genital tract were found up to 1939.

The most commonly accepted explanation of the histogenesis of these tumors is the theory that they develop from misplaced embryonic mesenchymal cells. These persist with potentiality for differentiation into the varied types of tissue found in the tumors. The theory of metaplasia or redifferentiation, previously held by some observers, has been practically abandoned.

There are essentially two types of dysontogenetic tumors. The first group has a myxomatous stroma, appearing almost edematous with cells widely spaced. The other group has a densely cellular make-up. In the lower genital tract, contrary to the upper, cartilaginous and osseous tissue is infrequent. A total of 10 cases of dysontogenetic tumors of the female lower genital tract have been treated at the Barnard Free Skin and Cancer, Barnes, and St. Louis Children's Hospitals. Three of these cases fall into the first group with myxomatous stroma and 7 into the second class. Table I shows this distribution.

Included in the first group are tumors commonly referred to as sarcoma botryoides. It is because of their myxomatous stroma that they possess the pink edematous polypoid appearance of grapelike clusters which gave them this title. These tumors are seldom reported in adults and are most common in children under the age of 2 years. They usually arise from the anterior portion of the vagina, although they grow so rapidly that the point or origin is frequently difficult to distinguish. Myoblasts and striated muscle are a usual component, but nerve bundles and cartilage may be found occasionally. Vaginal bleeding is usually the first symptom, since the neoplastic tissue is friable. However, growth is so rapid that severe pain from the stretching

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and pressure is sometimes present before much bleeding is evidenced. The growth is subject to infection and as a result of this and its variable blood supply, there is frequently much sloughing. Itching and burning of the vulva and vagina, pressure symptoms derived from the rectum and bladder, and actual protrusion of some of the tumor through the introitus occur in a few cases. Extremes of growth are usually present in the vagina before much spread by continuity occurs, even leading to occasional pressure necrosis. Distant metastases to the lungs and kidneys are late to develop.

TABLE I. CLASSIFICATION OF DYSONTOGENETIC TUMORS

<i>Myxomatous Stroma.</i> —	
1.	Sarcoma botryoides (childhood type)
2.	Mixed type with only partial myxomatous stroma (usually in adults)
<i>Densely Cellular Stroma (Everting and Infiltrating).</i> —	
1.	Sarcoma
2.	Mixed tumor

CASE 1.—A 7½-year-old white girl was seen in August, 1945, following two episodes of severe vaginal bleeding in the preceding 6½ weeks. Birth of the child had been uneventful, and mental and physical development had proceeded normally. On examination a pea-sized, soft, friable mass presented at the hymenal ring. When the hymen was broken, the vagina was found full of soft, polypoid, grapelike material. On microscopic examination tissue of a myxomatous stroma with many round cells of varied origin were found. Fibroblasts and leiomyoblasts predominated. The tissue was richly vascular with intact epithelium overlying it. The patient was given deep x-ray treatment and an application of radium in the vagina. Very little regression occurred, and in January, 1946, a second application of radium was made. A month later at another hospital intracavitary radium was applied within the vagina and within the uterine cavity. Following this she received palliative therapy until she died on Nov. 22, 1946, with bilateral massive pulmonary metastases.

Not all tumors possessing a myxomatous stroma fall within this group of botryoid tumors. Certain of them present a stroma that is only partially myxomatous and usually does not form grapelike clusters. Such tumors usually occur in adults and fail to show predilection for children. They also have a more insidious onset. Early encapsulation not only serves frequently to suggest the wrong prognosis but also makes even a gross diagnosis of malignancy difficult at times.

CASE 2.—A 29-year-old white woman was seen in August, 1938, six weeks after the enucleation of a small left labium nodule. The mass had increased in size rather rapidly after being present for a period of four years. On admission a 4.0 by 2.5 cm. nodular recurrence was present at the base of the previous scar and was fixed to the superficial tissue. A 1.5 cm. left inguinal nodule was also palpable. Microscopic examination of the tumor showed areas of dense and sparse cellularity. The tumor cells, which were separated into various-sized masses by a fibrous tissue network, were oval to spindle shaped and of varying individual sizes. Intracellular fat was demonstrated, and the tumor was diagnosed a liposarcoma. A unilateral vulvectomy with left Bassett dissection (superficial only) was done. Two months later widespread lung and bone metastases were demonstrable. Palliative treatment was given until she died in February, 1939.



CASE 3.—A 14-month-old white infant was seen in July, 1938, with a nontender walnut-sized mass of the labium majus. The baby had an uneventful delivery and developmental course. The mass was found well encapsulated when excised for biopsy. Microscopic examination of the tissue showed large atypical cells frequently vacuolated suggesting embryonic fat. Large nuclear masses with atypical mitoses were present. A myxomatous stroma was found with some smooth muscle. This represented a myxolipomyosarcoma by the descriptive terminology. Three weeks later the mass recurred and local x-ray was given. However, the tumor continued to enlarge and in November an inguinal mass was also noted. At this time the child seemed in a good stage of nutrition. In December the child was again admitted to the hospital with the mass the size of a lemon fixed to the deeper structures and extending to the fourchette. The right inguinal mass measured 2.0 by 4.0 cm., firm and fixed. A right vulvectomy with inguinal node dissection was done. By February the left inguinal nodes had enlarged and a mass was felt in the left vulva. A left vulvectomy with Bassett dissection was done and she was discharged from the hospital in fair condition. Serial x-ray studies of the chest and long bones up to this point had shown no metastases. In June, 1939, the patient had diarrhea and a distended abdomen. A mass was noted inferior to the right inguinal scar with induration half way to the umbilicus. A 3.0 by 2.0 cm. mass in the perirectal area was fixed and firm. The child died on Aug. 8, 1939, with no autopsy.

In the more densely cellular dysontogenetic tumors the stroma is mostly sarcomatous with the usual differentiation into spindle-cell and round-cell types. However, at times the classical mixed tumor picture appears and with even more diversified tissue types than the less cellular variety. They appear much as cervical cancers do, that is, either as everting or infiltrating types. As might be expected, the everting type, due to its vascularity as well as its exposure to more trauma, bleeds easily and is usually picked up earlier. This may be responsible also for its earlier regression following treatment. There are three cases presenting everting types, all of which were in adults.

CASE 4.—A 70-year-old white woman, with the history that two pedunculated tumors arising from the posterior vagina had been removed previously by cautery, first noticed the lesions two months earlier when bleeding had occurred. She was followed from September, 1948, to February, 1950, without recurrence. Then a papillomatous growth was noted in the suburethral region. Biopsies revealed an undifferentiated malignant tumor of the vagina and cervix, probably of mesenchymal origin. On microscopic examination very anaplastic cells occurred in sheets, cordlike structures, and even alveolar formation. Many mitotic figures, mostly abnormal, were found. This low degree of differentiation made classification of the tumor difficult. The patient received direct x-ray therapy to the vaginal tumor followed by application of radium. The lesion showed complete regression. In August a recurrence of the pedunculated tumor occurred on the right vaginal wall. The application of radium at that time again resulted in the regression of tumor. At the present the patient is still alive but has severe pain from an area of necrosis resulting from her therapy.

CASE 5.—A 61-year-old white woman was seen in February, 1945, after ten months of bloody vaginal discharge. She was found to have separate tumor masses located in the posterior fornix, the fossa navicularis, and the anterior vaginal wall just behind the urethra. These areas were indurated and presented an appearance of granulation tissue. All three were excised for biopsy and examination resulted in a diagnosis of sarcoma. On microscopic examination a combination of spindle-shaped cells and polygonal cells was present with many giant cells. Mitotic figures were not frequent; vacuolization was present in many cells. The patient received deep x-ray as well as transvaginal therapy to all three sites. The areas were soft after treatment but recurrence appeared within a month under the urethra and in the left vaginal wall. Cautery excision of both was

followed by application of a radium plaque. The tumor again seemed to regress but promptly recurred locally, and in the inguinal nodes as well. Node excision and further transvaginal x-ray were used with some regression. However, the patient shortly became bedfast and died with liver involvement on June 18, 1946.

CASE 6.—A 60-year-old white woman was seen in April, 1947, after nine years of bleeding from a small growth at the urethral meatus. It had been repeatedly cauterized by a local physician with silver nitrate and disappeared for periods of four to six months. Just before admission a biopsy of the small cauliflower tumor had shown malignancy. The soft noninfiltrating lesion arose from the posterior meatus, and on the right wall of the vestibule was another small, firm, fixed nodule. The tissue showed an undifferentiated connective-tissue tumor. It was composed of interlacing bundles of elongated cells with cigar-shaped nuclei. Large round cells and giant cells were often seen. Cytoplasmic vacuolization suggesting liposarcoma was present, but the differentiation was too poor for definite classification. The patient received a large dose of low voltage x-ray to the lesion with some regression, but immediately a recurrence was found on the right vaginal wall. This was similarly treated and disappeared. In October a mass in the left labium minus was treated with radium needles and regressed. Then a pedunculated anterior vaginal wall recurrence was treated with a radium plaque. By now the patient had a severe slough in the region of the vestibule. A positive right inguinal node was removed in July, 1948, and ten months later she received needles and a radium plaque to the anterior vaginal wall where much tumor persisted. Little change occurred, and she was not seen again before she died on April 10, 1950, with cerebral and pulmonary metastases.

Four patients presented infiltrating types of lesions. Bleeding in this group tends to be delayed until the overlying mucosa becomes necrotic. In general the prognosis is much worse.

CASE 7.—A 76-year-old white woman was seen in August, 1936, after two years of watery discharge and six months of irregular bleeding. She was in bad condition with much weight loss and urinary symptoms, including urinary retention of 4,000 c.c. On admission a large sloughing ulcer to the right of the urethral meatus measuring 4.0 by 3.0 cm. invaded the anterior vaginal wall leading to considerable associated edema. The left inguinal nodes were ulcerated and draining. Biopsy showed a sarcoma with round cells in cordlike arrangement and with a number of atypical mitoses. A few giant cells were present. The patient received needles and intracervical radium. A plaque was also placed over the inguinal area. She died September 6, without autopsy.

CASE 8.—A 79-year-old white woman was admitted in June, 1937, complaining of leukorrhea for six months and an episode of spotting a week before. On examination there was a 2.0 by 1.5 cm. sessile mass which extended somewhat into the posterior urethra with moderate necrosis and ulceration. The tumor had densely packed spindle-shaped cells with atypical mitoses. Occasional giant cells were present. She was treated with a gold plaque followed by gold seeds. The patient had no evidence of disease following treatment but died quite suddenly, Dec. 29, 1938, with no return of symptoms.

CASE 9.—A 64-year-old white woman was admitted in February, 1941, with a 2.0 by 1.5 cm. nodule on the right labium majus. She had had a curettage four months earlier for bleeding but no cancer was found. She had also had an x-ray menopause at the age of 47 because of bleeding. The mass felt cystic and well circumscribed at the time of excision. When cut open, it contained a gelatinous material. Microscopically, a densely cellular pattern of mostly spindle-shaped cells was found. They appeared to contain fat. A month later a partial vulvectomy and another dilatation and curettage were done. No microscopic tumor could be found in this specimen and the patient was free of tumor on her last examination.

CASE 10.—A 57-year-old white woman, 15 years past the menopause, was seen in February, 1950, after a week of vaginal spotting. On physical examination the cervix was normal but was partially obscured by a nonulcerated, 2.0 by 5.0 cm. nodular, irregular tumor on the posterior vaginal wall near the vault. Complete excision of the tumor was done for biopsy. It was well encapsulated with a fatty appearance and seemed to have been removed entirely except for a small portion of capsule at the base. Microscopic examination showed a bizarre pattern with no normal tissue. The epithelium was intact. A very anaplastic round-cell type prevailed with cytoplasmic vacuolization and many muscle and giant cells. A diagnosis of rhabdomyosarcoma of the vagina was made. Two weeks later more vaginal spotting occurred. Rectal pain also began, associated with a tender, soft, lobulated mass encircling the rectal lumen. In early March an operation was performed with an abdominoperineal approach in which resection of the rectum and lower sigmoid, hysterectomy including the posterior half of the vagina, and bilateral salpingo-oophorectomy were done. On examination no tumor could be found in the tumor specimen, and the mass previously described was entirely inflammatory. The patient has remained free of tumor since the operation.

As has been mentioned, the prognosis in all of the dysontogenetic tumors is extremely poor, and some have said that the diagnosis is open to question in any patient who lives over two years. The most disappointing thing is the false sense of security obtained from the good initial response of the early lesion either to radiation or surgery. Despite this response, repeated recurrences usually follow. They do not return at the same site as a rule but at some other site in the lower genital tract. It is almost as if there are cell rests of potentially malignant cells waiting their turn to become active. After a number of local recurrences, involvement of the other pelvic viscera or distant metastases occur, and the therapy becomes one of palliation. The seemingly more frequent involvement of the lymph nodes when the vulva is involved than the vagina may be only a matter of the more easy examination of these nodes.

The botryoid type of children's tumor follows about the same pattern but with more extensive vaginal involvement with each recurrence. This presents even more of an individual treatment problem since it is not readily available to much surgery in this age group and since the use of radium is mechanically difficult without some surgical excision.

Although many variations in the treatment have been used in these cases and other cases in the literature, it is surprising how seldom this is directed at the whole pelvis with its potentiality for multifocal recurrence. The use of local treatment to the primary lesion in the form of excision, local x-ray, or local radium may be a factor in the discouraging response to therapy. The use of more radical surgery as the primary treatment should be given a more adequate trial. In the same way, when radiation is the procedure, the application should be such that more irradiation to the whole pelvis is used. In a disease with such a poor prognosis every possible measure which might lead to improvement of the results should be tried.

### Summary and Conclusions

Dysontogenetic tumors or tumors of defective embryonic development is a term used to cover the group of sarcoma, sarcoma botryoides, and the various

mixed tumor types. These lesions fall into two main groups: those with a loose stromal cellular pattern, and those with closely packed cells. The group of cellular tumors can be divided into everting and infiltrating types. Ten cases are given representing these various classes.

Prognosis in cases of dysontogenetic tumor is extremely poor. However, treatment by more radical surgery or radiation applied to the whole pelvis for the primary lesion deserves a better trial. This would also eliminate the false sense of security frequently obtained by the good initial response of the tumors to local treatment.

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## **N-ALLYLNORMORPHINE: AN ANTAGONIST TO NEONATAL NARCOSIS PRODUCED BY SEDATION OF THE PARTURIENT**

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**I**T IS well known that the incidence of neonatal depression is greater if analgesics and sedatives are administered to the mother prior to delivery.<sup>1</sup> Nevertheless, most obstetricians and mothers are willing to accept this increased hazard in exchange for relative comfort during labor. Various agents have been proposed for the prevention or treatment of infant depression caused by narcotics, but none has proved completely satisfactory. The recent demonstration in man that n-allylnormorphine safely and effectively antagonizes respiratory and circulatory depression caused by opiates<sup>2, 3</sup> suggested the possible value of this compound for prevention of neonatal depression. The drug could be administered to the baby either through the placental circulation by predelivery injection to the mother or directly to the newborn shortly after delivery. This presentation is a report of an investigation of these uses of n-allylnormorphine conducted at the Hospital at the University of Pennsylvania.

### **Pharmacological Background**

N-allylnormorphine is a synthetic compound with a chemical structure closely allied to that of morphine. Data<sup>4, 5</sup> published in the pharmacological literature from 1941 to 1944 indicated the drug was capable of stimulating the respiration of animals depressed by morphine and when given prior to the administration of morphine prevented depression. Several clinical reports<sup>2, 3</sup> published within the past indicated that normorphine could antagonize respiratory and circulatory depression produced in man by morphine, meperidine, Dilaudid, Pantopon, and methadone, but was ineffective against narcosis caused by barbiturates, cyclopropane, and ethyl ether. Two case reports recently described this new opiate antagonist as an effective antidote in severe methadone poisoning.<sup>6</sup> No complications have been described from the use of normorphine in narcotized individuals. In normal human beings, however, the drug has proved a respiratory and circulatory depressant in its own right.<sup>2</sup>

### **Methods**

Data for this study were obtained from 1,100 patients admitted to the obstetrical service of the Hospital of the University of Pennsylvania for a 7½ month period, which began on Sept. 1, 1951. This group included all but 250 patients delivered at or after the twenty-eighth week of pregnancy. The 250 patients eliminated were those delivered by cesarean section or those who delivered vaginally with insufficient time to prepare and give the in-

jection within a reasonable period prior to delivery. For the statistical analyses presented, the following patients were excluded: those who received the drug less than 4 or more than 25 minutes before delivery; those in whom part of the solution had extravasated or in whom multiple injections had been made; and those parturients with twin pregnancies or obviously traumatic vaginal deliveries.

No attempt was made to standardize medication administered to patients in labor. The usual analgesics and sedatives included meperidine, Seconal, and scopolamine with average doses of 100 mg. meperidine, 200 mg. Seconal, and 0.4 mg. scopolamine. The highest total dose of meperidine was 375 mg. in a 7½ hour period. Barbiturates were rarely repeated. One series of patients received only meperidine for relief of discomfort and another small group, only morphine. Since the results obtained from these two groups were similar to those of the over-all study, they are included in our data and not considered separately.

Approximately one-half of the patients were given a solution containing 10 mg. n-allylnormorphine\* in 2 c.c. of normal saline intravenously. The remainder, serving as controls, received 2 c.c. of normal saline. The solutions were withdrawn from identical numbered ampules. No one in the delivery room knew whether the test drug or saline was being injected.

The most commonly used anesthetic agent was nitrous oxide with never less than 20 per cent oxygen. As weak a concentration of nitrous oxide as was compatible with satisfactory delivery conditions was employed. If adequate anesthesia could not be obtained with nitrous oxide, ether was added. A smaller number of patients were given caudal or spinal anesthesia or regional nerve block.

The standard procedure was as follows: Patients were moved from labor room to delivery room about 15 minutes before expected delivery. Two c.c. of normorphine or normal saline were injected into the antecubital vein of the parturient at an average of 10 minutes prior to delivery. A physician anesthetist, in attendance at each delivery, recorded pertinent observations on previously prepared data sheets. The time of the delivery of the infant's chin was carefully noted and recorded. Times were obtained from a stop watch or from a large wall clock. The seconds were counted until the first gasp of the infant and then until respiration or cry was established. Notes were made on the state of the infant's muscle tone and of oxygenation. Data were also recorded about the need for infant resuscitation, the development of secondary respiratory depression, and the maintenance of sustained crying.

An attempt was made to standardize the care of the child immediately after delivery. The usual procedure was to hold the infant's head downward and gently milk secretions from the trachea. The baby was then laid across the mother's abdomen while the umbilical cord was clamped and cut, and was then handed to the obstetrical nurse while the obstetrician turned his attention to the care of the mother. The nurse immediately placed the newborn in a crib of a Kreiselman resuscitative unit. Secretions were aspirated from the mouth and pharynx. If respiration was not established, the infant's posterior thorax was gently massaged. If, despite this, respiration did not start, intermittent positive oxygen by the mask-unit available with the Kreiselman resuscitator was instituted. The trachea was intubated if indicated. Some physicians or nurses tended to use oxygen more quickly than others. No attempt was made to discourage this individuality, but to clarify the need for the oxygen the physician or nurse was asked whether or not it was considered to be required for survival of the baby. The answer was recorded.

\*Supplied by Merck & Co., Inc., Rahway, N. J.

In addition to the above series of patients, 12 infants were given n-allylnormorphine directly into the umbilical cord vein. These were infants who failed to breathe for 5 to 10 minutes after delivery and who were believed apneic because of maternal opiate sedation. Infants depressed for any other cause were not considered suitable for such injections. In the 12 cases, 0.1 or 0.2 mg. n-allylnormorphine in 2 c.c. of normal saline was injected rapidly into the umbilical cord vein.

### Results

The results of this study are considered under two headings: first, the effect of normorphine on the baby; second, the effect of normorphine on the mother.

*Effects of Normorphine on the Newborn Infant.*—Five hundred thirty-two mothers received n-allylnormorphine prior to delivery, and normal saline was injected into 570 others who served as controls. There were 4 perinatal deaths (0.75 per cent) in the normorphine group and 3 (0.53 per cent) in the control group. Detailed studies of each fatality cast no suspicion on normorphine as a factor contributing to death. The over-all uncorrected perinatal death rate in infants 28 weeks or over who weighed 1,000 grams or over during the period of this study was 2.06 per cent.

In contrast to the depressant effect of n-allylnormorphine noted in normal man, its reaction on newborn infants resulted in no demonstrable depression. This conclusion, however, cannot be a final one because of the relatively small number of patients in our series. It is based on data from newborn infants delivered under regional anesthesia from mothers who received no sedation during labor (Table I). The time differences relating to onset and maintenance of respiratory activity between the normorphine and control groups are not statistically significant. Furthermore, in a group of infants born of mothers who received no antepartum sedatives but who were given nitrous oxide for delivery, there was no evidence of statistical significance that normorphine produced infant depression (Table II). However, these data do suggest that with nitrous oxide, n-allylnormorphine may cause a minor degree of infant depression.

TABLE I. EFFECT OF N-ALLYLNORMORPHINE ON NEONATAL RESPIRATION WHEN ADMINISTERED TO PARTURIENTS

*A. Without Opiate Sedation, With Regional Anesthesia*

	CONTROL	NORMORPHINE
Number of patients	23	15
Time to gasp (sec.)	18.5 $\pm$ 10.5	18.1 $\pm$ 13.1
Time to establish respiration (sec.)	25.1 $\pm$ 17.8	27.8 $\pm$ 21.3
Resuscitation		
Required	0	0
Prophylactic	0	1 (7%)

TABLE II. EFFECT OF N-ALLYLNORMORPHINE ON NEONATAL RESPIRATION WHEN ADMINISTERED TO PARTURIENTS

*B. Without Opiate Sedation, With Nitrous Oxide Anesthesia*

	CONTROL	NORMORPHINE
Number of patients	26	16
Time to gasp (sec.)	14.9 $\pm$ 10.9	22.7 $\pm$ 14.8
Time to establish respiration (sec.)	24.4 $\pm$ 15.4	34.9 $\pm$ 25.9
Resuscitation		
Required	0	0
Prophylactic	0	1 (6.3%)

Despite the possible existence of a mildly depressant action on un-narcotized newborn infants, normorphine definitely counteracted infant narcosis due solely to opiates used for maternal sedation. This attribute is demonstrated by data in Table III which are from patients given sedation consisting primarily of an opiate and who were delivered with regional anesthesia. The low incidence of resuscitation in newborns from mothers in the test group was striking and highly significant statistically when compared to the incidence in the control group. Further evidence of the potency of n-allylnormorphine's antagonistic action against opiates is shown in the same table by notably shorter periods from birth to gasp and from birth to establishment of respiration or cry in the test group as compared to the control group.

TABLE III. EFFECT OF N-ALLYLNORMORPHINE ON NEONATAL RESPIRATION WHEN ADMINISTERED TO PARTURIENTS

*C. With Opiate Sedation, With Regional Anesthesia*

	CONTROL	NORMORPHINE
Number of patients	48	46
Time to gasp (sec.)	27.0 $\pm$ 36.0	23.5 $\pm$ 15.0
Time to establish respiration (sec.)	72.4 $\pm$ 143.4	46.9 $\pm$ 11.0
Resuscitation		
Required	4 (8.3%)	1 (2.0%)
Prophylactic	8 (16.6%)	0

\*Highly significant statistically.

The ability of normorphine to decrease opiate narcosis was not evident in babies delivered under general anesthesia. When nitrous oxide was employed, the data from the control and test groups were almost identical (Table IV). When ether was added, infants in the test group actually were more narcotized (Table V). In the nitrous oxide group, this was probably due to the fact that a disproportionate percentage of patients was lightly sedated during labor. In babies from heavily sedated parturients (Table VI) who were given normorphine prior to delivery and nitrous oxide during delivery, the need for resuscitation and the time intervals were significantly lower than in the control group.

TABLE IV. EFFECT OF N-ALLYLNORMORPHINE ON NEONATAL RESPIRATION WHEN ADMINISTERED TO PARTURIENTS

*D. With Opiate Sedation and With Nitrous Oxide Anesthesia*

	CONTROL	NORMORPHINE
Number of patients	201	159
Time to gasp (sec.)	28.8 $\pm$ 26.7	30.1 $\pm$ 24.4
Time to establish respiration (sec.)	61.7 $\pm$ 83.7	61.4 $\pm$ 63.1
Resuscitation		
Required	17 (8.0%)	8 (5.0%)
Prophylactic	12 (6.5%)	11 (6.8%)

TABLE V. EFFECT OF N-ALLYLNORMORPHINE ON NEONATAL RESPIRATION WHEN ADMINISTERED TO PARTURIENTS

*Moderately or Deeply Depressed From Analgesics and Sedatives (Ether Anesthesia Excluded)*

	CONTROL	NORMORPHINE
Number of patients	97	86
Time to gasp (sec.)	37.6 $\pm$ 32.1	25.3 $\pm$ 21.3*
Time to establish respiration (sec.)	95.3 $\pm$ 107.1	63.2 $\pm$ 59.1*
Resuscitation		
Required	20 (22.6%)	10 (11.6%)*
Prophylactic	5 (5.1%)	5 (5.8%)

\*Statistically significant.



TABLE VI. EFFECT OF N-ALLYLNORMORPHINE ON NEONATAL RESPIRATION WHEN ADMINISTERED TO PARTURIENTS

*E. With Opiate Sedation and Nitrous Oxide-Ether Anesthesia*

	CONTROL	NORMORPHINE
Number of patients	136	85
Time to gasp (sec.)	31.8 $\pm$ 25.7	28.8 $\pm$ 26.8
Time to establish respiration (sec.)	90.0 $\pm$ 92.8	74.2 $\pm$ 78.7
Resuscitation		
Required	16 (11.8%)	10 (12.0%)
Prophylactic	10 (7.3%)	10 (12.0%)

\*Statistically significant.

The effects of n-allylnormorphine injected directly into infants were not studied until late in this investigation, consequently, it was given only to 12 infants. The results were the most dramatic of any obtained in our study and were excellent in 11 of the 12 cases. The one infant who did not respond satisfactorily was born of a mother who had been given normorphine 35 minutes prior to delivery. The effects in the other 11 were almost identical and are shown best by a typical case history:

S. L., a healthy white para iii, aged 25 years, at term, received 200 mg. Seconal, 100 mg. meperidine, and 0.4 mg. scopolamine 2 hours prior to delivery. At the time of delivery she was deeply depressed, responding only to pain. The infant failed to breathe after delivery. In spite of the usual resuscitative technique, including oxygen by intermittent positive pressure, the child remained apneic. Muscular tone was poor and color pallid. After 7 minutes of apnea, 0.2 mg. n-allylnormorphine in 2 c.c. of normal saline was injected into the umbilical cord vein. In 30 seconds respirations began and color and muscular tone improved. Within 2 minutes the child was crying vigorously.

*Effects of Normorphine on the Mother.*—There were no demonstrable maternal complications. A maternal analeptic effect was apparent in only a few sedated patients. However, several patients not given opiates experienced a cortical depressant effect manifested by hallucinations, crying, and complaints of muscular weakness.

Many of the patients who had had opiates with nitrous oxide and normorphine remained depressed for 15 to 30 minutes after the completion of the anesthetic. Most of these required a weaker concentration of nitrous oxide than was usually needed. There was no evidence that the drug retarded labor, adversely affected uterine tone, delayed delivery of the placenta, or increased blood loss.

#### Comment

The data reported herein indicate that n-allylnormorphine is a drug that can safely be employed in obstetrics by injection into either the mother or infant. It was not implicated in any of the infant deaths and did not significantly depress the infants if administered to normal unsedated mothers. It must be recalled, however, that the numbers of patients in these particular groups (Table I) were small and the results of a larger study might be different. In only one of the statistical comparisons were the data indicative of an increased degree of infant depression with normorphine. This was in Table VI which summarizes the observations on patients given opiates and nitrous oxide-ether anesthesia. In view of the well-known depressant effect of ether on newborn infants,<sup>7, 8</sup> the interpretation is difficult but the suggestion is apparent that normorphine should not be administered to mothers given ether anesthesia.

Suggestive evidence was obtained that, if normorphine was administered too far in advance of delivery, effectiveness of the drug disappeared and the infants were actually slower in breathing than were the controls. It was difficult to establish the exact time interval, but it appeared to be about 25 minutes. This explains why patients who had their injection more than 25 minutes before delivery were excluded from the analysis. The optional interval between injection and delivery seemed to be 5 to 15 minutes.

Our data clearly show that n-allylnormorphine is a potent agent and has a place in modern obstetrical practice. The figures in Table III (patients with opiate sedation and regional anesthesia) indicate a desirable effect. Experiences with direct injections into apneic infants were impressive, but the small number of patients does not permit unqualified endorsement. Evidence obtained from moderately or deeply depressed parturients given opiates and nitrous oxide anesthesia was statistically favorable to normorphine, but not nearly so impressive as the data from the two groups mentioned.

The undesirable effects of normorphine apparent in this study were the increased number of resuscitations required in the group given ether for anesthesia, and the cortical depressant effects noted in unsedated mothers. The latter observation would not be a real objection to the clinical use of the drug in obstetrics, nor would a slight depressant effect in infants born of unsedated mothers, because it is obvious that an opiate antagonist would not be employed if opiates had not been given to the mother. A prolongation of narcosis following nitrous oxide anesthesia would definitely be undesirable, since it might increase the hazard of respiratory obstruction or aspiration of vomitus.

No attempt has been made to correlate the total dose of opiate administered to the mother with the effectiveness of normorphine because of the variable response to a given dose of opiate. Some of the most profound depressions we have seen have been with relatively small doses of analgesics and in contrast some mothers were reasonably alert after large doses of opiates and were delivered of well-oxygenated infants who cried immediately. It might, however, be worth while to correlate time of administration of opiates with effect of normorphine. This we have not attempted to do.

No effect has been made to change the dose of normorphine. In our study a single dosage was used for uniformity of data. It is reasonable to believe that the deeper the maternal depression the larger the dose of antagonist required. Therefore, it is probable that had we used larger doses of normorphine for the heavily depressed parturients, a more significant effect on the infants might have been apparent. However, these larger doses would probably produce an analeptic effect on the mother, a result not particularly desirable immediately before delivery.

Our experience suggests that normorphine will have its most practical clinical value when injected directly into the infant. The delay permits evaluation of the baby, his need for an opiate antagonist, and the presence of factors which might contraindicate administration of the drug with its potential depressant effects. Normorphine is a specific antagonist to opiates and not a panacea for the treatment of asphyxia neonatorum. It should not be administered to infants apneic from any cause other than opiate narcosis, for example, from birth trauma, anoxia from nuchal cord, etc. When used under such circumstances normorphine might deepen the depression. Where inhalational anesthetics and opiates administered to the mother are probably the cause of infant depression, normorphine might be considered after artificial ventilation has removed most of the anesthetic from the baby's blood stream. The optimal dose for infant use appears to be 0.2 mg. in 2 c.c.

of normal saline. We have not tried larger doses because they have not been necessary. It would seem wise to avoid unnecessarily large doses primarily because of the danger of secondary depression.

To recapitulate, our data suggest that the principal values of normorphine in obstetrics are: (a) In the treatment of apnea neonatorum due to maternal opiate sedation. In this circumstance it is best employed in 0.2 mg. doses in 2 c.c. of normal saline and injected into the umbilical cord vein. (b) In the prevention of neonatal depression in infants born of mothers depressed with opiates and given regional anesthesia or nitrous oxide for delivery. Here the optimal dose is 10 mg. injected intravenously into the mother 5 to 15 minutes prior to delivery. In deeply depressed mothers, 15 mg. might be more efficacious.

### Summary

1. The use of n-allylnormorphine in the prevention of asphyxia neonatorum due to opiates has been investigated in a series of 1,100 parturients.

2. When 10 mg. of this drug was injected intravenously into mothers prior to delivery there was no depression of the infants in the control group. There was, however, a significant reduction in the need for resuscitation and times required to gasp and breathe in infants born of mothers who had opiate sedation.

3. The efficacy of the drug was reduced when the mothers received nitrous oxide anesthesia, but there was still a significant shortening of time to gasp and to breathe as well as a decreased incidence of the need for resuscitation in infants born of mothers clinically classified as moderately or deeply depressed.

4. The opiate antagonistic effects of normorphine are not apparent in infants born of mothers who had ether anesthesia.

5. One-tenth to 0.2 mg. of the drug was injected into the umbilical cord vein of 12 infants apneic 5 to 10 minutes after delivery. The result in 11 was a prompt institution of respiration, improvement in color and muscular tone, followed by sustained crying.

We would like to express our appreciation to Frances Hetzell, R.N., and to Dr. George Hart, for their technical assistance in this investigation.

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## THE INTRINSIC FETAL MORTALITY OF CESAREAN SECTION\*

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THE techniques of modern obstetrics have been successful in markedly reducing maternal mortality rates. Fetal mortality has not decreased proportionately, and until recently less thought and attention have been given to the problems of the fetus. Basic knowledge of the physiology and pathology of the fetus is lacking, and it is relatively difficult to classify and evaluate all of the diverse influences which play a part in fetal survival.

There has been much discussion as to the proper role of cesarean section in obtaining maximum fetal salvage. Whether it is justifiable to extend the indications for cesarean section to obtain a possible decrease in fetal mortality, can be answered better after analysis of the fetal loss inherent in the operation of cesarean section itself. Many authors have cited the safety of cesarean section to the mother, but fetal mortality has been noted to be high.<sup>1, 2</sup> It is accepted that premature delivery has been the greatest single cause for this high mortality, particularly when combined with intrauterine anoxia. Cesarean section is often chosen, however, as the most feasible method of delivery in these situations. The obstetrician is often faced with the decision as to whether delivery by cesarean section in a premature period offers a greater or lesser chance of the survival of the fetus than the continuation of the pregnancy in an unfavorable intrauterine environment.

In surveying the cesarean sections done at the Philadelphia General Hospital during the 10-year period, 1941 through 1950, it was evident that during this period neonatal mortality and stillbirth figures did not progressively decline (Fig. 1), a finding which is in keeping with reports published by other clinics. During the period mentioned, the cesarean section fetal loss averaged 14.4 per cent, a higher mortality than has generally been reported.<sup>3-5</sup> In interpreting these figures, however, it must be remembered that the Philadelphia General Hospital serves a large number of persons from a socially and economically impoverished section of the population. As will be brought out later, a large percentage of these patients have received no prenatal care and often enter the hospital for the first time presenting some relatively advanced pathologic process.

It was considered possible that there would be certain lessons to learn from a statistical analysis of a series of cesarean sections offering such a high fetal mortality. It was also considered possible that a breakdown of these cases could be carried out in such a way as to demonstrate which portion of this over-all mortality could be considered intrinsic in the operation of cesarean

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section and which portion was the result of the complications which necessitated this type of delivery.

### Material

The material analyzed represents a series of 611 consecutive cesarean sections performed at the Philadelphia General Hospital between Jan. 1, 1941 and Dec. 31, 1950. There were five sets of twins, bringing the total babies delivered to 616. All of these babies weighed over 1,000 grams. In this series, there were 45 stillborns and 44 neonatal deaths, representing a total fetal loss of 14.4 per cent.

During this same period there were 22,033 total stillborn and live births, therefore the over-all cesarean section incidence was 2.8 per cent. It was interesting to note that there was no tendency toward an increasing incidence through this period. In 1941, the incidence was 1.9 per cent, climbing to 3.8 per cent in 1945, but falling back to 2.6 per cent in 1950.

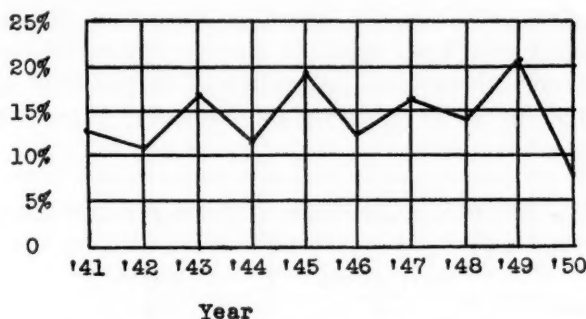


Fig. 1.—Fetal mortality from cesarean section at the Philadelphia General Hospital.

In order to evaluate the fetal loss intrinsic in the operation of cesarean section, it was necessary to divide the material into two groups: The first group consisted of those cases in which there were no known maternal complications which might cause an increased fetal mortality. It was readily apparent that in some cases the stated indications for section did not reflect all of the factors which might influence fetal survival and the cases were individually studied for complications. The second group consisted of those cases in which known maternal complications might affect fetal survival. Inasmuch as the relative survival of the premature infant was of considerable interest, prematurity or premature labor, per se, was not considered a factor in dividing the cases into the two groups.

#### *Group 1.—Uncomplicated Sections.*

There were 352 sections in this series which as defined above showed no maternal complications. Indications for these sections were: previous section, 215; cephalopelvic disproportion, 117; and miscellaneous, 20.

There were two sets of twins, bringing the total number of babies delivered to 354. There were no stillbirths but there were twelve neonatal deaths; a gross mortality of 3.4 per cent.

As is generally the case, the pathologic findings in these twelve babies were not particularly helpful in determining the cause of death despite a high percentage of autopsy examinations. Eleven of these babies were signed out as prematurity with the various complications of prematurity such as atelectasis, bronchopneumonia, ventricular hemorrhage, etc. One full-term infant in this group died of bronchopneumonia resulting from an obstructing mediastinal cyst and could not be considered a salvageable infant from an obstetric standpoint. It is difficult to say what various more specific pathologic diagnosis could have been found in this group if a greater knowledge of neonatal pathology was available.

As would be expected, the greatest single factor in fetal survival was the weight of the baby. (Table I.) In this period there were 292 full-term babies delivered by cesarean section in the absence of maternal complications. In this group there was only one fetal death. This baby, as mentioned above, was not salvageable because of congenital abnormalities. Fetal mortality in the premature group, however, increased markedly as the degree of prematurity increased. In the forty-eight babies weighing between 2,000 and 2,500 grams, there was a mortality of 6.3 per cent. In the ten babies with a weight between 1,500 and 2,000 grams, there was a mortality of 40 per cent, while in the four babies in the 1,000 to 1,500 gram-weight category, there was 100 per cent mortality.

TABLE I. FETAL WEIGHT AND MORTALITY IN UNCOMPLICATED CESAREAN SECTION

WEIGHT	TOTAL BABIES	DEATHS	MORTALITY (PER CENT)
1,000-1,500 grams	4	4	100.0
1,500-2,000 grams	10	4	40.0
2,000-2,500 grams	48	3	6.3
Over 2,500 grams	292	1	0.3

It is of interest to note the cause of the prematurity in this uncomplicated group of cesarean sections. In five cases, section was performed because of the onset of uterine contractions in patients who had had previous cesarean section. In one patient there was pain over the old section scar, but no rupture was found at the time of operation. In three cases section was performed because of premature rupture of the membranes in patients who had had previous cesarean sections. In three cases there was no apparent reason as listed in the records, for the section having been premature and apparently represented errors in judging the gestational period.

In order to evaluate the effect of prenatal care in this group, the patients were arbitrarily divided into three classes for the purpose of analysis. In Class A were those patients who had attended the Prenatal Clinic four or more times, the last visit being in the last month of pregnancy. Class B included those patients who had registered in clinic but did not meet the aforementioned criteria. Those patients who had received no prenatal care were listed as Class C. As will be seen in Table II, prenatal care did nothing to increase fetal salvage in the absence of maternal complications. The 215 patients in Group A

sustained a fetal loss of 3.2 per cent. The eighty-eight patients in Group B sustained a fetal loss of 4.5 per cent, while the forty-eight patients in Group C suffered no fetal mortality.

TABLE II. THE EFFECT OF PRENATAL CARE IN UNCOMPLICATED CESAREAN SECTION

GROUP	CASES	BABIES	NEONATAL DEATHS	MORTALITY (PER CENT)
A	215	216	7	3.2
B	88	88	4	4.5
C	48	49	0	0.0

It has become a generally accepted principle built on wider experience than this article covers, that regional anesthesia leads to a greater fetal salvage than does general anesthesia.<sup>6-8</sup> In this series, however, no statistically significant mortality difference could be demonstrated as can be seen in Table III. There was a 3.3 per cent fetal loss in those sections done under general anesthesia and a 3.0 per cent fetal loss in those sections done under regional anesthesia. In the earlier years of this series, general anesthesia was used for nearly all cesarean sections, but in later years, regional anesthesia has been used almost exclusively except where felt to be contraindicated.

TABLE III. THE EFFECT OF ANESTHESIA IN UNCOMPLICATED CESAREAN SECTION

ANESTHESIA	CASES	NEONATAL DEATHS	MORTALITY (PER CENT)
Ether	60	2	3.3
Cyclopropane	60	2	
Nitrous oxide	1	0	
Spinal	217	7	3.0
Local	11	0	
Caudal	3	0	
Epidural block	1	0	

#### *Group 2.—Complicated Cesarean Sections.*

As would be expected those sections in which a maternal complication had developed led to a much higher fetal mortality. There were 259 sections classified in this group with four sets of twins, bringing the total number of babies delivered to 263. There were forty-five stillbirths (17.4 per cent) and thirty-two neonatal deaths (12.4 per cent), an over-all mortality of 29.7 per cent.

The pathologic findings in this group of neonatal deaths were also of little help. Of the thirty-two deaths, twenty-six were in premature babies. Twenty-four of these were signed out simply as prematurity with its various conditions. One of the other premature babies showed multiple congenital abnormalities, and one showed hemorrhagic disease of the newborn infant. There were six full-term babies, two of which showed multiple congenital abnormalities and were probably not obstetrically salvageable. The other four showed nonspecific anoxic changes, probably the result of impaired placental circulation.

The causes of fetal loss in these complicated cesarean sections are listed in Table IV. There were thirty-seven babies delivered with an indication of previous cesarean section and thirty-eight delivered with an indication of cephalo-

pelvic disproportion. These conditions in themselves were not considered to carry an intrinsic fetal risk, but in each case, listed in this group, there was some additional factor, such as toxemia, infection, etc., which caused them to be placed with the complicated sections. In the group of 37 sections done because of previous cesarean section, there was one stillbirth due to a high spinal anesthesia with maternal shock. There was one neonatal death due to congenital abnormalities plus intrauterine infection. In the group of thirty-eight sections done for cephalopelvic disproportion, there were eight stillbirths, of which six were due to intrauterine infection, one to prolapsed cord, and one to premature separation of the placenta. There was one neonatal death due to intrauterine infection.

TABLE IV. FETAL LOSS IN COMPLICATED CESAREAN SECTION

INDICATION	NO. CASES	NO. BABIES	STILL-BORNS	CAUSE OF STILLBIRTH	NEONATAL DEATHS	CAUSE OF NEONATAL DEATH
Previous section	37	37	1	1 high spinal	1	1 infection and cong. deform.
Cephalopelvic disproportion	38	38	8	6 infection 1 prolapsed cord 1 premature separation	1	1 infection and prematurity
Placenta previa	46	46	4	Anoxia	11	2 anoxia 8 anoxia, premat. 1 premat., hem. disease
Premature separation	42	43	18	Anoxia	9	2 anoxia 6 anoxia, premat. 1 prematurity, cong. deform.
Malpresentation	18	18	3	2 impaction 1 cardiac decomp.	0	
Inertia uteri	11	11	2	2 infection	2	1 anoxia, cong. deformity 1 toxemia and prematurity
Nonconvulsive toxemia	22	24	1	Anoxia, toxemia	2	Anoxia, toxemia, prematurity
Convulsive toxemia	11	12	1	Anoxia, toxemia	2	Anoxia, toxemia, prematurity
Diabetes mellitus	8	8	1	Diabetes	1	1 diabetes
Ruptured uterus	3	3	3	Anoxia	0	
Heart disease	8	8	0		2	2 prematurity
Miscellaneous	15	15	3	1 maternal shock 1 monster 1 post-moterm section	1	1 prematurity

Most of the remaining fetal loss of this series was apparently due directly to the indications for which these sections were performed. Placental pathology resulted in the greatest fetal loss. It is in this group particularly that lack of prenatal care and delay in seeking hospitalization played a major role. In forty-six cases of placenta previa four stillbirths and eleven neonatal deaths resulted. All but two of these neonatal deaths were associated with prematurity; one of these premature babies had hemorrhagic disease of the newborn. Among the forty-three babies delivered because of premature separation of the placenta there were eighteen stillbirths and nine neonatal deaths. Cesarean section was utilized much less in recent years as a method of delivery in premature separation than during the earlier years of this series.



Malpresentation of the fetus was the indication for section in eighteen cases. This group included only those cases in which the primary indication for the section was the malpresentation. There were fifteen cases of transverse lie, two brow presentations, and one face presentation. There were three stillbirths, two due to impaction of neglected transverse lie, one due to cardiac decompensation in the mother.

Inertia uteri was the indication for section in eleven cases resulting in two stillbirths due to intrauterine infection, and two neonatal deaths, one due to congenital abnormalities plus a forty-hour labor and one due to a combination of maternal toxemia, prematurity, and a forty-hour labor.

Maternal toxemia was the primary indication for section in thirty-three cases with delivery of thirty-six babies. There were twenty-four babies delivered because of nonconclusive toxemia, with one stillbirth and two neonatal deaths. Twelve babies were delivered from mothers with convulsive toxemia, with one stillborn death and two neonatal deaths. These babies tended to be quite premature and show nonspecific anoxic changes.

There were eight sections done for diabetes mellitus with one stillborn and one neonatal death. There were eight sections done for cardiac disease in the mother with no stillbirths but two neonatal deaths due to prematurity. These eight sections for cardiac disease were done in the early years of this period.

There were three sections done because of rupture of the uterus with three stillbirths resulting. One of these ruptures was spontaneous in a patient with no previous cesarean section. The other two occurred through previous cesarean section scars. Asymptomatic ruptured uterus after previous cesarean section was noted in two cases at the time of operation.

There were fifteen sections done for various miscellaneous complications. There were three stillbirths in this unclassified group, one due to a gross monstrosity, one after post-mortem section, and one following maternal shock of undetermined etiology. One neonatal death due to prematurity resulted after section for chronic glomerulonephritis.

TABLE V. THE EFFECT OF PRENATAL CARE IN COMPLICATED CESAREAN SECTION

GROUP	CASES	BABIES	NEONATAL DEATHS	PER CENT	STILLBIRTHS	PER CENT
A	100	101	4	4.0	13	12.9
B	67	69	10	14.5	9	13.0
C	90	91	16	17.6	23	25.3

The heavy contribution of intrauterine infection to our fetal mortality is apparent in the above figures. This complication occurred in a total of eighteen cases in this series and resulted in ten stillbirths and one neonatal death, a mortality of 61.1 per cent, a higher percentage mortality than any other single complication. It should be added that in many instances these patients were infected at the time of admission to the hospital.

Unlike the previous statistics, prenatal care did much to reduce fetal mortality in cases which developed these maternal complications (Table V). Patients receiving no prenatal care sustained a neonatal death rate of 17.6 per cent

and a stillbirth rate of 25.3 per cent which was reduced to 14.5 per cent and 13.0 per cent for Group B clinic patients and 4.0 per cent and 12.9 per cent for Group A as previously defined.

### Discussion

During recent years there has been a marked increase in the incidence of cesarean section for fetal indications as reported by many clinics. Such an increase has been associated with a lowering of fetal mortality.

This series of cesarean sections differs from most series recently reported because of a lower cesarean section incidence, a higher fetal mortality, and a greater incidence of relatively severe complications resulting in large measure from inadequate prenatal care.

The type of statistical breakdown used in this series indicates that abdominal delivery carries little danger to the full-term fetus in the absence of maternal complications. Under the same conditions, the mortality of the premature infant was higher in this series than would be expected after uncomplicated vaginal delivery.

The factor of weight in the survival of these prematures totally overshadowed all other considerations such as anesthesia and prenatal care. When cesarean sections which were done because of maternal complications were analyzed, the fetal mortality became purely a function of the complication under analysis.

The absolute survival rate for each weight class of prematures depends in large measure upon the quality of the pediatric care available. During recent years a pediatrician has been present at all cesarean section deliveries to give prompt care to the baby. It is felt that this measure coupled with newer pediatric techniques and more intensive care of the premature infant will result in improved premature mortality statistics in the future.

The authors wish to express their appreciation to Thaddeus L. Montgomery, M.D., for his aid and encouragement in the preparation of this paper.

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### Discussion

DR. W. A. REISSTEIN.—Obstetricians have for many years thought and taught that "danger to the life of the baby" is an indication for termination of the pregnancy or labor. Until recently only lip service has been paid to this indication. The added danger of abdominal delivery to the mother has militated against such attempts at salvage of the unknown, unborn infant. We now know that increased maternal salvage depends on the prevention of critical situations and on intervention before maternal endurance is exhausted.

The infant organism, on the other hand, must continue to face critical situations until certain signs and symptoms of distress become manifest. Intervention is given consideration, therefore, at a time when the infant's opportunity for survival has been seriously compromised.

The authors have made an important contribution. Their study helps to dispel the fear that cesarean section, *per se*, increases infant mortality. The concept that maximum infant survival is dependent on the preconditioning effects of uterine contractions and passage through the birth canal seems to be invalidated at least in the case of mature or nearly mature infants. It is of interest that their study seems to indicate that the type of anesthesia associated with the cesarean section is not a significant factor in fetal survival.

As indicated by the authors there are many unknowns in the causation of intrauterine and neonatal mortality. However, my experience with the Stillbirth Committee of Philadelphia leads me to believe that an immediate increase in fetal salvage is possible in that group of infants at or near maturity who are lost during labor or shortly thereafter as a result of difficult and dangerous vaginal procedures applied because cesarean section is considered to be intrinsically more prejudicial to the infant and to the mother. We have become aware that such vaginal procedures can and do threaten the maternal organism. Dr. Taylor and Dr. Ward have, by their study, indicated that the infant organism can be better served by abdominal delivery in such instances.

Serious consideration should be given to the earlier recognition of malpresentations, prolapsed cord, premature rupture of the membranes with associated abnormality, and aberrations of uterine forces. The careful vaginal examination must come back into its own in spite of the inconveniences of aseptic technique. Earlier recognition of these conditions will preclude the haste precipitated by signs of fetal distress noted, all too frequently, by an attendant other than the responsible obstetrician.

These comments are, by no means, intended to condone the unwise or excessive use of cesarean section. Principles and practices applied to increase the chances of the infant presently endangered must not too greatly decrease the opportunity for survival of its future siblings. As noted by the authors, prior cesarean section can be associated with and often is the cause of premature labor, premature rupture of the membranes, premature separation of the placenta, and premature termination of the pregnancy by the obstetrician. In justice to the mother, her intrauterine infant and her future progeny, abdominal delivery is chosen only after alert and conscientious judgment so dictates. In its application, meticulous techniques of uterine surgery are applied to that portion of the uterus least likely to interfere with future implantation, placentation and uterine growth.

## CAN WE CORRECTLY ASSESS CEPHALOPELVIC DISPROPORTION?\*

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**H**ISTORICALLY, the prophylaxis of dystocia due to contracted pelvis really started 100 years ago with the work of Michaelis, who has been described as the "Father of Pelvimetry." Although his name is associated with external pelvimetry, the importance of which is now discounted, we must not forget that Michaelis' lasting contribution was not his method of pelvimetry, but his fundamental conception that it was worth while trying to detect contracted pelvis before labor had produced some grave and urgent complication. Once it was realized that the prevention of dystocia was a better objective than the treatment of it, the path was open for devising improved methods of detection. Although Smellie, in the eighteenth century, measured the diagonal conjugate of the pelvis digitally, the development of elaborate methods of internal pelvimetry took place in the early part of the present century; this development was the expression of a desire to obtain more accurate information about the shape and size of the pelvis, but until the end of the first decade of this century little or no account was taken of the part played by the fetal head in the production of dystocia. The problem was stated in terms of pelvic size. Then, largely as the result of the lead given by Munro Kerr, dystocia came to be regarded not simply in terms of pelvic capacity, but rather as the problem of the relative sizes of the fetal head and the mother's pelvis. The problem was restated, and the introduction of the term cephalopelvic disproportion is a landmark in the evolution of our ideas on this subject. Clinicians now tried to detect, not contracted pelvis, but disproportion. Artificial pelvimeters went out of fashion, and it was declared that "the fetal head is the best pelvimeter." It was at this time that the engagement of the fetal head in a primigravida began to be generally recognized as the best guarantee that her labor would not be complicated by bony obstruction. This guarantee which gradually came to be acknowledged from about 1915, left a group of primigravidas in whom nonengagement of the head at the end of pregnancy indicated an uncertain outcome of labor. This group has given rise to difficulties ever since, and we are still very far from having solved the problem of making a certain diagnosis. From 1915 to 1925 various clinical procedures were developed for trying to assess the degree of disproportion between the head and the pelvis in cases in which the head was not engaged. These methods, typified by what in Great Britain was known as Munro Kerr's method, all aimed at estimating the amount by which the fetal

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head seemed to overlap the symphysis; and, as a result of this clinical estimate, the obstetrician decided either not to interfere, to induce premature labor, or to perform cesarean section before the onset of labor.

Now, this method of dealing with cases of disproportion was quite logical if the premises were sound, but gradually people began to doubt their ability to estimate overlap, to forecast the degree of molding, or to judge the degree of flexion of the head. Once the doubt had been raised, the whole basis of treatment became suspect, and it was slowly realized that many of the patients who had previously had inductions of premature labor, or even cesarean section, subsequently delivered themselves spontaneously of babies often bigger than their first-born. The period 1925 to 1930 witnessed a complete revolution with the introduction of trial labor, and it soon became obvious that, in all but the more severe degrees of pelvic contraction, the necessity for cesarean section in cases of suspected disproportion could be properly determined only after a trial of labor.

We cannot appreciate the changes which made possible the introduction of trial labor, without digressing to consider what were the factors that operated between 1925 and 1930 to eliminate the special dangers of cesarean section performed late in labor. The factor which generally receives most of the credit is the general introduction of the lower-segment operation; there is not any division of opinion about the superiority of the lower-segment, over the upper-segment, operation, when the patient is in labor; but there was a second factor which played an important—I believe the most important—part in diminishing the hazards of cesarean section performed after the onset of labor, viz., the gradual appreciation of the common sources of severe puerperal infections. Let us not forget that cesarean section can, under proper conditions, be safely undertaken after labor has been in progress for many hours or even days, not mainly because of the introduction of the lower-segment operation, but rather because we now realize the precautions we must take to prevent infection of the birth canal during the trial of labor.

By 1930, most centers in Great Britain had practically discarded induction of premature labor as a method of treatment of suspected disproportion in primigravidas, and had adopted trial of labor as the routine method of dealing with all but the most marked cases of contracted pelvis. It seemed, at last, that we had found the ideal method, and that when we performed cesarean section after a trial of labor, we had really proved the presence of a serious degree of disproportion. Furthermore, the abandonment of induction of premature labor in primigravidas did not result in an increase in the number of cesarean sections, a clear indication that most of the inductions, and possibly some of the cesarean sections before labor, had been quite unnecessary in the past.

Unfortunately, trial of labor, with the experience of the last 20 years, has proved not to be so simple an answer to the problem of disproportion as had been hoped. It carries with it problems of its own, and the conduct of a trial of labor still demands the exercise of clinical judgment. The more evidence we can collect before passing judgment, the less often are we likely to make a wrong diagnosis. For this reason the adoption of trial of labor as a routine

method has been a reason for finding out more, not less, information about all the factors in mother and fetus that may have a bearing on the outcome of labor. Twenty years ago it seemed as if the adoption of trial of labor might render unnecessary any detailed information about the size of the fetus or the size and shape of the pelvis. The very contrary is, in fact, the case, and in the past twenty years more attention has been directed to the conformation of the pelvis than at any other time in the history of obstetrics.

By far the most prolific contributions in recent years to the clinical study of cephalopelvic disproportion have come from radiography. All these methods supply us with facts about pelvic size and shape that cannot be obtained by other methods, and to that extent they are useful in the management of suspected disproportion by the method of trial labor; but they do not supply the answer to the fundamental question of whether or not a head will pass through a pelvis. When we first began to employ trial labor most of us hoped that it would enable us to estimate accurately the amount of disproportion in doubtful cases. We have now had sufficient experience with the method to enable us to judge its measure of success or failure in solving the clinical problem; everyone is aware that trial labor has its limitations, but it is worth while to try to evaluate these limitations, and to try to see how far we succeed in making accurate estimates of disproportion with all the modern methods and aids that are now at our disposal.

TABLE I. TOTAL MIDWIFERY PRACTICE OF GUY'S HOSPITAL, 10 YEARS (1934-1938 AND 1946-1950, WAR YEARS OMITTED)

	GROUP A	GROUP B	TOTAL (GROUPS A AND B)
Total deliveries	10,093	2,024	12,117
Maternal deaths	16	8	24
(Per 1,000)	(1.6)	(4)	(2)
Stillbirths	283	110	393
(Per 1,000)	(28)	(55)	(32)
Infant deaths	117	54	171
(Per 1,000)	(11)	(27)	(14)

TABLE II. INCIDENCE OF DISPROPORTION AMONG 12,117 DELIVERIES. CASES IN WHICH OBSTETRIC INTERFERENCE WAS UNDERTAKEN ON ACCOUNT OF DISPROPORTION

CESAREAN SECTION AFTER TRIAL OF LABOR	CESAREAN SECTION WITHOUT TRIAL OF LABOR	FORCEPS DELIVERY	INDUCTION OF PREMATURE LABOR	CRANIOTOMY	TOTAL
65	118	74	61	8	326
(0.54 per cent)	(0.98 per cent)	(0.6 per cent)	(0.5 per cent)	(0.06 per cent)	(2.66 per cent)

In order to get an over-all picture of the importance of cephalopelvic disproportion in the group of patients we deal with at Guy's Hospital in London, I have taken the total deliveries of the hospital for a period of 10 years. Class A comprises patients who are domiciled in a small compact district in the immediate neighborhood of the hospital, so that it represents a relatively unselected group of patients. Class B is made up of patients domiciled elsewhere who form a highly selected group, and many of whom come to the hospital because of some real or anticipated difficulty. Table I is given merely to supply

a background against which the cases of disproportion have to be considered.

Table II shows the cases in which some obstetric interference was undertaken on account of cephalopelvic disproportion, some degree of which was present in 2.66 per cent of all the cases.

Let us now examine the group in which cesarean section was performed after a trial labor, with the object of finding out how often the trial can be said to have proved definitely that gross disproportion did, in fact, exist. There are two—admittedly very crude—ways in which the extent of a trial of labor can be expressed in figures: either by the number of hours that the labor is allowed to continue, or by the degree of dilatation of the cervix when the trial is terminated by cesarean section. Fig. 1 gives this information for the cases in this series.

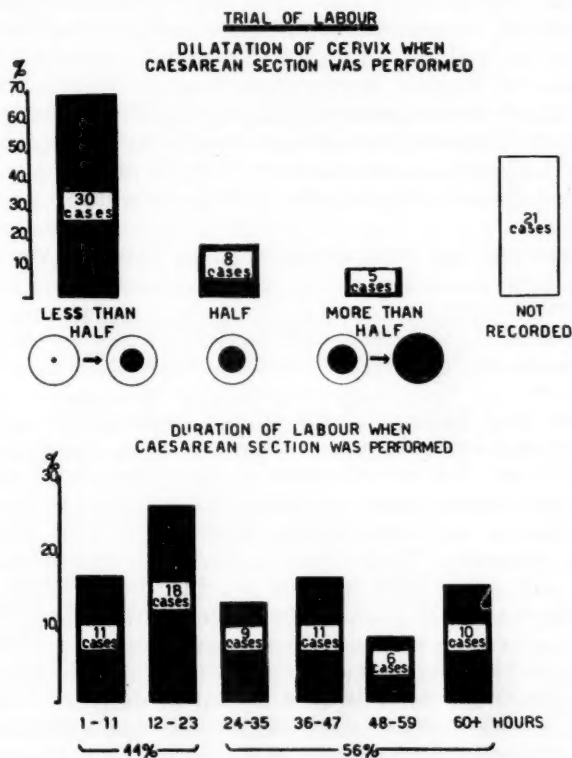


Fig. 1.

We are often asked, "How long, or to what stage of labor, should a trial of labor be allowed to proceed, before it can be deemed to be decisive?" I am not prepared to say what should be done; I can say what, in fact, was done in the group of patients I am describing. The diagram shows quite clearly that although, in 56 per cent of cases, labor was allowed to proceed for more than 24 hours, the cervix was less than half dilated in nearly 70 per cent when the trial was terminated by cesarean section. The contrast between the long duration of the labor, and the tardy dilatation of the cervix is very striking, and it emphasizes the part played by disproportion in contributing to the clinical condition of inertia with all the attendant tedium and danger of a long first stage of labor. Disproportion is so often associated with "inertia" or "functional rigidity of the cervix" that the trial of labor turns out to be a test, not chiefly of pelvic capacity, but often to a large extent of the capacity of the cervix to

dilate. Are we ever justified during the conduct of a trial labor in concluding that there is gross bony obstruction at a stage of labor when the cervix is only half dilated or less? Undoubtedly in some cases we are justified in coming to a decision; failure of the head to descend, progressive increase in the caput succedaneum; and perhaps also the development of edema of the anterior lip of the cervix; these and other signs sometimes justify a diagnosis of gross disproportion long before the cervix is fully dilated, and in these cases we can properly regard the trial of labor as a true test of disproportion. In other cases, however, there may be an indication to terminate the labor at a stage before we can assert that we have proved the presence of pelvic incapacity. The commonest of such indications is maternal exhaustion, mental and physical, associated with slow dilatation of the cervix; a less common indication is asphyxia in the fetus. No one will deny that often these are good indications for terminating the trial by cesarean section; they are good indications because the objective is to deliver a living child by the safest method. We must admit, however, that when we employ cesarean section in these circumstances in the course of a trial labor, we sometimes abandon (quite properly) the attempt to test pelvic capacity. I have analyzed our results in Table III. Taking all the circumstances into account, it has been possible to pick out what seemed to be the major indication for terminating the trial in each case.

TABLE III. INDICATION FOR TERMINATING TRIAL OF LABOR BY CESAREAN SECTION

DISPROPORTION CONSIDERED TO BE PROVED	MATERNAL DISTRESS	FETAL ASPHYXIA	TOTAL
40 (61 per cent)	16 (24 per cent)	9 (14 per cent)	65

It will be seen that in only about 60 per cent of the cases of trial labor which were terminated by cesarean section were we reasonably satisfied that we had proved the need for interference on the grounds of disproportion. In the remaining 40 per cent of cases, although the cesarean section may have been none the less justifiable, we were still in doubt as to how much, or how little, disproportion was present. These figures give us a numerical estimate of the limitations of the method of trial labor in solving the problem of disproportion in its general application. We must not forget that, in the case of outlet contraction, the position is even worse. There is only one way of proving the existence of insuperable contraction at the pelvic outlet, that is, to wait until the second stage of labor, to apply the forceps, and to fail to deliver. The disastrous consequences of such a test are sufficient reason for not adopting it; and a real trial of labor is not applicable when the capacity of the pelvic outlet is in doubt.

If we now turn to the group of cesarean sections which were performed without a preliminary trial of labor we must examine critically the evidence of disproportion upon which the justification for the operation rested. It is surprising to find such a high proportion of elective cesarean sections in the practice of a hospital where trial of labor is accepted as the routine method of assessing disproportion in primigravidas. Table IV sets out in more detail the factors which led to the decision to perform cesarean section in these cases without a preliminary trial of labor.

TABLE IV. CESAREAN SECTION FOR DISPROPORTION WITHOUT PRELIMINARY TRIAL OF LABOR

REASONS FOR PERFORMING CESAREAN SECTION	NUMBER OF CASES
Gross pelvic contraction diagnosed before labor	18
Previous difficult delivery with death of infant	21
Previous cesarean section after trial of labor	62
Additional complications	17
Total	118



Let us be generous and accept straightaway the 18 cases diagnosed as gross disproportion, and the 21 cases in which a previous stillbirth or very difficult delivery was attributed to disproportion. Let us assume that clinical disproportion was reasonably well proved in these two groups. In the two remaining groups, however, no such broad assumption can be made. The group in which some additional obstetric difficulty was present is obviously a doubtful one so far as proved disproportion is concerned, and the cesarean section was admittedly undertaken partly for some other indication. The group in which failure of a previous trial labor was accepted on the next occasion as the basis for the diagnosis of disproportion is also open to doubt; we have already seen that a trial of labor in suspected disproportion is terminated by cesarean section in about 40 per cent of cases, not because disproportion has been proved, but because the trial has to be abandoned prematurely on account of maternal exhaustion or fetal asphyxia. If we subtract 40 per cent of the cases of previous cesarean section after trial labor, and all the cases in which some other obstetric complication was present we are left with about 70 out of a total of 118 (60 per cent) planned cesarean sections for "disproportion" in which gross disproportion had been reasonably proved.

In the group of cases which I have analyzed, out of 12,117 confinements, forceps delivery was employed in the presence of some disproportion in 73 cases. The obstetric forceps is not, of course, a proper method of treating disproportion of any but the most minor degree, and the vast majority of the cases in this group presented no anxiety. In the main, they represent a group of patients in whom pelvic capacity had been correctly assessed as not grossly inadequate before or during labor, and successful delivery with moderate traction was clearly a vindication of the diagnosis and treatment. But there is a minority of patients in whom the outcome of labor was not successful, and these must be examined in more detail as they will contain the cases in which an important degree of disproportion had not been correctly anticipated.

TABLE V. FORCEPS DELIVERY IN WHICH THE DELAY IN LABOR WAS CONSIDERED TO BE DUE TO DISPROPORTION

NUMBER OF FORCEPS DELIVERIES ASSOCIATED WITH DISPROPORTION	STILLBIRTHS AND NEONATAL DEATHS	INTRACRANIAL HEMORRHAGE
74	11	6

The over-all fetal and neonatal mortality is influenced by many factors other than disproportion, but the deaths from intracranial hemorrhage (total 6) must be taken as an index of the extent to which we fail correctly to assess serious disproportion in these cases. In 6 cases we wrongly assessed the amount of disproportion as being of negligible degree, a mistake which cost the life of the infant. In this type of case, in which we think that a forceps delivery is a reasonable operation to embark upon, only to find that it is unexpectedly difficult when we come to perform it, we so often discover—albeit, too late—that the final difficulty is due to contraction at the pelvic outlet. Contraction confined to the brim or cavity is seldom associated with this mistake, because when the dystocia is in the upper pelvic strait, the course of trial labor is so obviously unfavorable that we are never tempted to try to deliver with the forceps. The failure of trial of labor to solve the problem of outlet contraction has already been referred to, and is responsible indirectly for most of the difficulties—and some of the disasters—that appear in this group of forceps deliveries.

Under modern conditions there should be no place for craniotomy in the treatment of cephalopelvic disproportion. Apart from cases of hydrocephalus,

and perhaps also outlet obstruction with a dead fetus, it is doubtful whether craniotomy is ever a safer operation for the mother than the alternative of cesarean section. Among the 12,117 deliveries in this series, craniotomy was performed 16 times, and the indications for the operation are set out in Table VI.

TABLE VI. CRANIOTOMY

INDICATION	NUMBER OF CASES
Hydrocephalus	9
Disproportion	
Fetus dead	8
Fetus alive	0
Total	17

The only group which concerns us in the present discussion is that in which the indication for craniotomy was disproportion. Although craniotomy was never performed on a living fetus, in 7 of the cases the fetus was alive at the beginning of labor. If a degree of disproportion sufficient to call for a craniotomy on the dead fetus had been recognized at the beginning of labor, there can be no doubt that cesarean section would have been chosen as the method of delivery. The loss of infant life, and the hazards to which the mothers were exposed in these 7 cases must therefore be attributed ultimately to the failure to detect a serious degree of disproportion.

*Induction of Premature Labor.*—Since the introduction of trial of labor in 1925, induction of premature labor to anticipate disproportion has been confined mainly to multigravidas in whom a previous difficult delivery was thought to have been due to some degree of disproportion; but even in this type of case induction of premature labor has been employed less and less frequently in recent years. If, in a primigravida, in spite of a good application of the forceps, excessive traction has to be used to deliver the fetus, it might seem reasonable to assume that there must be some cephalopelvic disproportion, and to forecast that a future delivery will be similarly difficult if the fetus is of similar size. It is on this assumption that induction of premature labor at a subsequent pregnancy is carried out, but in practice the assumption is often found to be incorrect. The results of induction of premature labor in this group of 12,117 deliveries are shown in Table VII.

TABLE VII. INDUCTION OF PREMATURE LABOR FOR SUSPECTED DISPROPORTION

TOTAL CASES	STILLBIRTHS	FORCEPS DELIVERY	SPONTANEOUS DELIVERY
61	5	11	50

Among the 61 cases in which induction was undertaken, spontaneous delivery occurred in 50. It may be that if some of these cases had been allowed to go to term, disproportion might have resulted, but it would probably have been serious in only very few, and one cannot escape the conclusion that probably in the majority of these 50 cases the interference was unnecessary. On the other hand, the induction of premature labor for suspected disproportion was followed by a difficult forceps delivery resulting in the death of the fetus in 5 cases, so this last figure must be an index of the extent to which we failed to circumvent serious disproportion when, in fact, it did exist.

We are now in a position to take stock of our attempts to assess cephalopelvic disproportion.

First, let us consider those cases in which we made a timely diagnosis of disproportion so that we were able to choose what we considered to be the best type of interference. These cases comprise all the cesarean sections, and all the inductions of premature labor. In both these groups we have already tried to discover how often we really proved the presence of disproportion. The results of this critical review are summarized in Table VIII.

TABLE VIII. CASES IN WHICH A DIAGNOSIS OF SERIOUS DISPROPORTION WAS MADE AND ACTED UPON

	CESAREAN SECTION		INDUCTION OF PREMATURE LABOR	TOTAL
	AFTER TRIAL OF LABOR	WITHOUT TRIAL OF LABOR		
Serious dispro- portion proved	40	70(?)	5*	115
Serious dispro- portion not proved	25	48(?)	56	129
Total	65	118	61	244

\*Proved, but not avoided.

It would be foolish to take these figures literally. They can be nothing more than a measurement of how often an opinion was held, but at least they should make us very careful in asserting our ability to diagnose cephalopelvic disproportion. Taken at their face value they mean that with all the modern methods of pelvimetry at our disposal, and with the use of trial labor to guide us, an assertion of gross disproportion is proved to be correct in about half of the cases. In the other half, it may or may not be correct, but we have no means of knowing when we are mistaken.

Second, let us consider those cases in which we formed and acted upon the opinion that there was not any serious cephalopelvic disproportion. These cases comprise the whole of the group of 12,117 deliveries after the cesarean section and induction cases have been subtracted. Thus, in 11,873 patients we concluded that there was not any gross disproportion, and labor was conducted on this assumption. How often were we wrong? Our mistakes are to be found among the craniotomies for disproportion when the fetus was alive at the beginning of labor, and the cases of fatal intracranial hemorrhage following forceps delivery for disproportion with or without previous induction of labor. These cases are summarized in Table IX.

TABLE IX. CASES IN WHICH A DIAGNOSIS OF NO SERIOUS DISPROPORTION WAS MADE AND ACTED UPON

DIAGNOSIS VINDICATED BY RESULT	SERIOUS DISPROPORTION ENCOUNTERED	TOTAL
11,855	Craniotomy 7 Intracranial } 18 hemorrhage 11	11,873

These figures are in striking contrast to those of Table VIII. Taken at their face value they mean that when we conclude there is not any serious disproportion, we are wrong in our diagnosis about once in every 650 cases.

### Summary

One can summarize these conclusions very simply in general terms by saying that the diagnosis of pelvic adequacy is, on the whole, easy and very seldom mistaken; the cost of the rare mistake is generally the life of the fetus,

and sometimes also a greatly increased hazard to the mother. On the other hand, the diagnosis of pelvic inadequacy is difficult and often mistaken; we do not know how often we are mistaken but we have not any good evidence that errors are less than 50 per cent. The cost of a mistake in this group is generally an unnecessary cesarean section, or perhaps an unnecessary induction of labor, neither of which is entirely without danger to the mother or fetus.

It is not my purpose here to attempt to suggest how best to strike a balance in this dilemma. The problem is one to which every practicing obstetrician has applied himself. The different values which different individuals place upon the many considerations involved are reflected in the different practices which are adopted by various people. I have tried merely to state the problem, and my excuse for taking so long in the statement is that I believe a clear statement is a necessary preliminary to any improvement. Since pelvic radiography has been developed, and since it has become so easy to diagnose pelvic contraction, many people have been mesmerized into believing that it is easy correctly to forecast cephalopelvic disproportion. It can do no harm to show that, in 1952, some of us still find it very difficult.



## INDUCTION OF LABOR IN ECLAMPSIA

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**M**OST obstetricians agree that an interruption of pregnancy is indicated during the intercurrent phase of eclampsia. This is the period of relative improvement following convulsions, when no further convulsions occur, the blood pressure falls, and the albuminuria diminishes. "The improvement is only temporary," to quote Stander,<sup>1</sup> "and after a few days the blood pressure begins to rise, the albumen to increase and the general condition to become less satisfactory. In such circumstances labor should be induced. . . ." It is during this intercurrent phase that obstetricians are faced with the problem of terminating the pregnancy. If labor should occur spontaneously or the fetus should die in utero, the maintenance of the patient in an adequate state of sedation usually suffices until the fetus is expelled. However, if interference is indicated, a medical induction of labor (rupture of membranes, castor oil, etc.) or a cesarean section must be employed. The former is unpredictable and the latter is not without danger. The purpose of this paper is to describe a method of terminating the pregnancy of an eclamptic patient by inducing labor with Pitocin.

### Case Reports

CASE 1.—P. R. was a 26-year-old para 0, gravida ii (abortion at 2 months in 1946), who was admitted to the hospital in the twenty-sixth week of pregnancy on Nov. 10, 1947, following her first clinic visit, with the diagnosis of severe pre-eclampsia. The blood pressure on admission was 230/120, and a 4 plus albuminuria and generalized edema were present. She was asymptomatic but had noticed the edema for the past four days. The fundus was somewhat smaller than a 26 weeks' gestation. The fetal heartbeat was regular and no uterine contractions were noted. The vertex was presenting and was floating. Sedation and diuretics were administered. After twenty-four hours the blood pressure had become relatively stable at 170/100. Thirty-five hours after admission the patient suddenly complained of blindness and a convulsion which lasted four minutes followed. The blood pressure rose to 240/140. Fundoscopic examination revealed many small retinal hemorrhages. Following sedation the blood pressure was stabilized at 160/130. A vaginal examination was performed in bed. The cervix was found to be partly effaced but undilated. The fetal head was still floating. Membranes were ruptured with an orange stick. After four and one-half hours no uterine contractions were noted. Phenobarbital sodium, 2 grains, and morphine sulfate,  $\frac{1}{4}$  grain, were administered, and one hour later 3 minims of Pitocin were given intramuscularly. Labor started shortly thereafter. Uterine contractions became strong and regular, occurring every  $1\frac{1}{2}$  to 2 minutes and lasting 30 to 40 seconds. Two hours and forty minutes after Pitocin had been administered a 2 pound,  $\frac{1}{4}$  ounce living infant was delivered. During labor the blood pressure varied between 160 and 170 systolic and 130 and 140 diastolic. The patient remained well sedated throughout the entire labor. The baby survived for 23 hours. The patient made an uneventful recovery and was discharged on Nov. 20, 1947, with blood pressure stabilized at 170/110. A 1 plus albuminuria was present and there was no edema.

Four years later the patient was seen again with a 10 weeks' gestation. Although her blood pressure was quite labile, it remained within normal limits throughout her pregnancy. Her delivery was uneventful.

CASE 2.—S. H. was a 25-year-old primigravida, 26 weeks pregnant, who had not attended the prenatal clinic. The patient was awakened at 4 A.M. on Aug. 13, 1950, with a severe headache. An ambulance was called at 10 A.M. and en route to the hospital the patient had a tonic convulsion, frothed at the mouth, and lost consciousness. She had regained consciousness when she arrived at the hospital but in the admitting room she had another convulsion. Following the second convulsion her blood pressure was 140/85. When she arrived on the ward it was 164/110. Examination revealed a lethargic, listless patient who was, however, oriented. A 1 plus pretibial edema and 4 plus albuminuria were present. The uterus was at the level of the umbilicus; the vertex was presenting and was unengaged. The fetal heartbeat was regular. The cervix was thick and undilated. The patient was not in labor. Sedation was administered and during the first 48 hours she remained relatively quiet. Her blood pressure varied from 120 to 180 systolic and from 80 to 130 diastolic. Urine output for the first 24 hours was 300 c.c. and for the second 24 hours was 695 c.c. It was noticed at this time that the uterus was very sensitive and contracted with slight stimulation. An attempt was made to rupture the membranes but the cervix was uneffaced and did not permit entry. At 10 A.M. on August 15, morphine sulfate,  $\frac{1}{4}$  grain, and Seconal,  $1\frac{1}{2}$  grains, were administered. Forty minutes later, 1 L. of 10 per cent glucose solution with 0.25 c.c. of Pitocin was administered intravenously at the rate of 30 drops per minute. Uterine contractions began immediately and occurred every  $1\frac{1}{2}$  to 2 minutes. The blood pressure was 140/100 prior to the induction and remained relatively stable around 160/100 during labor. The patient was completely insensible to the contractions. Two hours later the cervix was 50 per cent effaced and 2 cm. dilated. The membranes were ruptured with an orange stick. After six hours the cervix was 75 per cent effaced and 3 cm. dilated. The vertex was at minus 3 station. Two Allis clamps were applied to the scalp and a 1 pound weight was attached. The Pitocin infusion infiltrated shortly thereafter, and it was decided to permit labor to continue without it. However, the uterine contractions diminished and finally ceased in two hours. The vertex had descended to the spines. One minim of Pitocin was given intramuscularly at 8 P.M. and 2 minims were given at 9 P.M. Uterine contractions became regular and strong after the first dose, and fourteen hours after labor was initiated a 1-pound, 14 ounce infant was delivered. The baby survived only a short while. The original sedation was supplemented with two injections of morphine sulfate,  $\frac{1}{4}$  grain, and the patient remained insensible to contractions throughout labor and delivery. The patient signed out of the hospital on the fifth postpartum day with a blood pressure of 150/110. No albuminuria or edema was present. No follow-up was obtained on this patient.

CASE 3.—C. M. was a 19-year-old primigravida who was admitted to the hospital on Nov. 25, 1950, in the thirty-first week of gestation. She had not attended the prenatal clinic. The day before admission the patient noticed a severe headache and puffiness of the face. The morning of admission she complained of partial blindness, and at 11 A.M. she had a convulsion at home. Another convulsion occurred at 1 P.M. and another at 2 P.M., at which time an ambulance was called. When she was admitted to the hospital the blood pressure was 186/100; a 1 plus pretibial and facial edema and 4 plus albuminuria were present. The uterus was enlarged to 3 fingerbreadths below the xiphoid process. The fetal heartbeat was regular. Rectal examination revealed the vertex to be presenting and to be unengaged. The cervix was thick and undilated and no uterine contractions were felt. The patient was heavily sedated and was maintained in an adequately restful state until November 29. The blood pressure during this period varied between 160 and 210 systolic and 130 and 180 diastolic. No further convulsions occurred. Intake and output were satisfactory. The edema subsided and the albuminuria decreased to 1 plus. On November 29 a sterile vaginal examination revealed the cervix to be about 75 per

cent effaced with no dilatation. The vertex was still unengaged. The membranes were ruptured with an orange stick. Four hours later no uterine contractions were noted and the patient was sedated with Nembutal, 3 grains intramuscularly, and Demerol, 100 mg. by hypodermic. One-half hour later an infusion of 1,000 c.c. of 10 per cent glucose solution with 0.25 c.c. of Pitocin was started. Labor began immediately. After two hours the cervix was completely effaced and was 1 cm. dilated. The vertex had descended to plus 2 station. The fetal heartbeat remained regular. Six hours later the cervix was 7 cm. dilated. A saddle block was administered and fifty minutes later a 3 pound, 12 $\frac{1}{4}$  ounce infant was delivered in good condition. The duration of labor was nine hours. The blood pressure had risen slowly during labor to 204/170 at which point the saddle block was administered. The pressure then dropped to 150/122.

The mother and baby did well post partum. Edema and albuminuria subsided rapidly, and on the day of discharge the blood pressure was 120/86. The patient delivered a second child sixteen months later. She remained completely asymptomatic throughout this pregnancy and had an uneventful delivery.

CASE 4.—C. D. was a 28-year-old markedly obese para ii, gravida iii, clinic patient who was admitted on Feb. 1, 1951, during the thirty-sixth week of gestation for severe pre-eclampsia and hypertensive vascular disease. The patient delivered her first child at Lincoln Hospital in March, 1948. During the prenatal course she maintained a blood pressure around 140/90. Prior to delivery the blood pressure rose to 210/138 and a 4 plus albuminuria and 3 plus pretibial edema appeared. She was admitted to the hospital, membranes ruptured artificially, and labor and delivery followed with no complications.

The second pregnancy terminated in September, 1949. During this prenatal course she maintained a blood pressure around 140/90, with no albuminuria or edema. She delivered rapidly with no complications.

During the course of the present pregnancy, the patient was admitted to the hospital in the thirty-third week because of a sudden rise in blood pressure from 140/90 to 180/110. The urine was negative and no edema was present. During her hospital stay the patient was found to have a mild case of diabetes which was controlled by diet. She was discharged to the clinic after seventeen days with a blood pressure of 140/96. One month later, in the thirty-seventh week, the patient was again admitted to the hospital for a sudden rise in blood pressure to 200/116, a 4 plus albuminuria, and a 2 plus pretibial and facial edema. The urine also contained 3 plus glucose. The fetus was estimated to weigh around 5 pounds and the fetal heartbeat was regular. The cervix was soft, thick, and undilated. The vertex was presenting and was floating. Sedation was administered and the diabetes was controlled with diet and small doses of regular insulin. The urine never contained more than a trace of acetone. Approximately twenty-four hours after admission the patient had a short clonic convulsion, following which the blood pressure was 180/120. The urine contained 3 plus albumin and no sugar. Sedation and a glucose infusion were administered. The response was good. After a six-day period no further convulsions had occurred, the blood pressure had dropped to 150/100, and the albuminuria had decreased to 2 plus. The diabetes remained well controlled. On the seventh day a vaginal examination revealed no change in fetus or cervix and no uterine contractions had occurred. One hundred mg. of Demerol was administered intravenously, and a few minutes later a 1:1,000 Pitocin infusion was started. Labor began shortly thereafter. After five and one-half hours the Pitocin infusion stopped because of infiltration. The cervix was effaced and 6 cm. dilated. The vertex was at minus 2 station. The membranes were ruptured artificially. It was decided not to continue the Pitocin infusion as labor was progressing well without it. After six hours of labor the patient delivered a 5 pound infant in good condition. Prior to and throughout labor the blood pressure varied from 150 to 160 systolic and from 100 to 120 diastolic.

The postpartum course was uneventful and the patient was discharged on the thirteenth postpartum day with a blood pressure of 164/116, a trace of albuminuria, and no edema. She did not return to the follow-up clinic.



CASE 5.—M. L. was a 35-year-old primigravida clinic patient, 37 weeks pregnant, who was admitted to the hospital on Nov. 4, 1951, in a semicomatose state following a convulsion at home. Her prenatal course had been essentially normal. Four days prior to admission she attended the prenatal clinic and a rise in blood pressure from 110/80 to 118/96 and 1 plus albuminuria were noted. Bed rest was prescribed and the patient advised to return to the clinic in two days. She failed to keep her appointment and four days later was brought to the hospital by ambulance following the convulsion. On admission the blood pressure was 170/120; a 4 plus albuminuria and a 2 plus generalized edema were present. The patient was semicomatose and extremely restless. The uterus was compatible in size to the period of gestation. The fetal heartbeat was regular. Rectal examination revealed the vertex presenting and not engaged. The cervix was uneffaced and undilated. The patient was not in labor. After heavy sedation the blood pressure dropped to 140/110. However, the urinary output was only 275 c.c. in the first twenty-four hours and 245 c.c. in the next eighteen hours despite diuretics. On November 6 the patient began vomiting coffee-ground material. The edema had increased to 4 plus in the extremities and fine scattered râles were heard in the chest. Microscopic urinalysis revealed many red blood cells and granular casts. Blood pressure at this time was 162/115, pulse 124, respirations 20, and the temperature spiked suddenly to 104° F. A diagnosis of lower nephron nephrosis and early pneumonitis was made. One-third grain of Pantopon was administered at 11 A.M., and at 11:30 A.M. a 1:1,000 Pitocin infusion was started. Mild uterine contractions were noted immediately. Five hours later the cervix admitted one finger and membranes were ruptured artificially. Seven hours after the Pitocin infusion was started the cervix was 5 cm. dilated, the vertex at minus two station in right occipito-posterior position, and the fetal heartbeat was regular. The blood pressure was 150/115, pulse 112, respirations 20. The temperature remained at 104° F. despite antibiotics. Thirteen hours after induction a normal 6 pound, 3 ounce infant was delivered by Szanzoni rotation and extraction. A saddle block was given for anesthesia. Following delivery the blood pressure was 158/130, pulse 96, and respirations 20. The temperature returned to normal on the first postpartum day and diuresis occurred on the second. The patient was discharged on the twentieth postpartum day with blood pressure of 140/90, negative urine, and no edema.

The patient was seen in the clinic one month later with a blood pressure of 120/80, negative urine, and no edema.

### Comment

There are several interesting facts to be noted in these five case reports. The most important is the response of the eclamptic patient to Pitocin. There is no doubt but that labor was successfully induced and completed in all five patients. This occurred despite the fact that certain conditions were present that would under normal circumstances thwart an attempt to induce labor. Two patients were in the sixth month of pregnancy, two in the seventh, and one in the ninth. None was in labor prior to induction. In only two cases could the cervix be dilated sufficiently to rupture the membranes before induction. This measure did not induce labor after four and four and one-half hours respectively. The presenting part was not engaged prior to induction; however, no contraindication to vaginal delivery existed. Two of the primiparas with no softening or effacement of the cervix required fourteen and thirteen hours of labor before delivery. The other two primiparas with partially effaced cervixes delivered in two hours and forty minutes and nine hours, respectively. It was possible to rupture membranes prior to induction in the former.

The eclamptic process frequently initiates labor spontaneously regardless of the term of gestation. There is, however, an optimal time to initiate labor for which Nature is sometimes unprepared. It has been shown that maternal and fetal mortality increases with the duration of eclampsia. Dieckmann<sup>2</sup> has



found a 7 per cent maternal mortality if delivery is effected in less than 2 hours after the first convulsion, which increases to 28 per cent if over 21 hours elapse. Chesley and Somers<sup>3</sup> found a 57.2 per cent fetal mortality when delivery is delayed more than 3 days following a convulsion, and a 25.8 per cent mortality if the fetus is delivered within 3 days. This is not to be construed to mean that immediate delivery following an eclamptic convulsion is essential. Results can be most disastrous if the proper time is not selected to induce labor. The consensus among obstetricians is to wait 48 to 72 hours after the convulsions have been controlled before attempting to initiate labor, and, failing this, a cesarean section should be performed (Mengert,<sup>4</sup> Reid<sup>5</sup>). In severe eclampsia, Dieckmann<sup>6</sup> advises waiting as little as 6 hours after the last convulsion before attempting delivery.

We have followed this pattern in our treatment. We have induced labor in our patients only after we were certain that the convulsive stage was well controlled or only when complications (renal shutdown and pneumonitis) led us to expect no amelioration of symptoms. As we know, this intercurrent stage may persist for only a few days and may be followed by a recurrent eclampsia with its high mortality rate. Reinberger and Russell<sup>7</sup> have indicated the symptoms marking the end point of intercurrent eclampsia. These are: (1) marked oliguria or anuria, (2) increase in temperature, pulse and respirations, (3) evidence of pulmonary edema, and (4) increased cyanosis. Rather than await these symptoms, we believe an attempt should be made to induce labor with Pitocin. Prematurity, intact membranes, and "unripe" cervixes have thus far been no barrier to induction, probably because the eclamptic process would have precipitated labor spontaneously sooner or later. But there was an optimistic note in delivering these mothers early in their state of eclampsia. The hope of obtaining a living infant rather than anticipating a fetal death was present.

### Summary

Five cases of eclampsia have been presented in which labor was successfully induced and completed by the use of Pitocin.

The use of Pitocin induction is recommended only during intercurrent eclampsia or possibly for eclampsia with complications, provided the eclamptic symptoms can be controlled for an adequate time to permit labor and delivery.

The author wishes to thank Dr. William Godsick, Director of the Department of Obstetrics and Gynecology, Lincoln Hospital, and Dr. David Zakin for their helpful criticisms during the preparation of this paper.

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**POSTNATAL GROWTH AND DEVELOPMENT OF INFANTS BORN  
AFTER DIETHYLSTILBESTROL ADMINISTRATION  
DURING PREGNANCY\***

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THE prophylactic administration of diethylstilbestrol in pregnancy to prevent those accidents associated with progesterone deficiency was introduced in 1946 by Smith, Smith, and Hurwitz.<sup>1</sup> The success of this treatment in preventing abortion,<sup>2</sup> reducing the incidence and severity of late pregnancy complications, and increasing fetal salvage<sup>3, 4</sup> has led to its continued and extensive use in this hospital. Previously reported clinical studies indicated that the newborn infants of stilbestrol-treated mothers exhibited no deleterious effects from the Smith and Smith regime. In fact, weights and lengths of infants born prematurely to stilbestrol-treated mothers exceeded those expected at their gestational age,<sup>3, 4</sup> a finding presumably related to the reduced fetal loss observed. Because all of these data covered only the prenatal and immediately postnatal periods, the present study of postnatal development was undertaken.

**Material and Plan of Study**

The records accumulated by Drs. O. W. and G. Van S. Smith on patients in this hospital provided a large series of infants born between October, 1947, and December, 1948, to presumably normal primiparous mothers. Prenatal, delivery, and neonatal data were available from 387 such pregnancies in which stilbestrol was administered and from 555 equally well-studied synchronous controls.<sup>4</sup> As these numbers were too large to allow any careful follow-up of all resulting infants by physical examination 2 to 3 years later, the infants delivered spontaneously but before expected term were selected for study. These patients comprised essentially the treated and control groups described in Tables II to V and Figs. 3 to 7 of Reference 4. This selection not only provided infants from treated and control pregnancies in groups sufficiently small so that most could be located and brought into the clinic for examination. It also narrowed the clinical material to patients who, by virtue of their premature birth, might display any effects of stilbestrol upon growth or development more clearly than would the less rapidly growing infants of full-term birth. Stilbestrol medication, always discontinued at the thirty-fifth week of pregnancy, was not significantly curtailed by the degree of prematurity of these infants.

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All mothers, treated or control, of infants born more than 14 days before term were invited to bring them to the clinic for examination to evaluate the results of premature birth. Table I indicates the success achieved in locating and examining the patients. Entirely by chance the location of a smaller percentage of control infants resulted in fairly comparable numbers from both groups.

TABLE I. PREMATURELY BORN INFANTS OF PRIMIPARAS TREATED WITH STILBESTROL DURING PREGNANCY, AND OF SYNCHRONOUS CONTROL PRIMIPARAS

	FROM TREATED PREGNANCIES	FROM CONTROL PREGNANCIES
Number of infants sought	42*	60*
Number not located	5	19
Moved elsewhere but information furnished	2	2
Died after discharge	2	0
Examined	33 (79%)	39 (65%)
Ages at examination	2 3/12 to 3 6/12 yrs.	2 1/12 to 3 7/12 yrs.
Sex	20 ♀, 13 ♂	19 ♀, 20 ♂
Negro infants	2	3

\*The inclusion of twin infants resulted in slightly different numbers from those appearing in tables of Reference 4.

TABLE II. PREGNANCIES DURING 2 TO 3½ YEARS SUBSEQUENT TO THAT ORIGINALLY TREATED OR USED AS CONTROL

	TREATED	CONTROL
Number of mothers whose infants were examined	32*	39
<i>Subsequent Pregnancies:</i>		
Normally completed	14	12
Terminating in premature birth	0	4
Terminating in miscarriage	0	4
Incomplete at time of study	4	1
Total	18	21

\*One mother had twins.

The children were examined and their histories taken by two of the authors (M. C. and G. H.), who consulted with each other before recording any unusual finding. The "treated" or "control" status was not known at this time. The socioeconomic status of the family, the diet and vitamin intake of the child, and the history of illnesses were recorded as factors which might independently influence growth. Data as to dentition and motor and intellectual progress were of necessity dependent on the mother's memory, but the error introduced would presumably be similar in both groups of infants. Skeletal age was estimated from roentgenogram of the wrist.

### Results

The two deaths among the "stilbestrol" infants after their discharge from the hospital deserve comment before presentation of results. One infant of 4 months, apparently normal and gaining weight well since birth, was found suddenly dead in his carriage. The Medical Examiner's diagnosis (without autopsy) was death from acute respiratory infection. The other infant died after 5 months of apparently normal growth from an acute gastroenteritis.

The diagnosis was made clinically and at autopsy, which showed nothing else of significance, at the Children's Hospital. Neither death would appear pertinent to the present investigation.

Analyses of the relative socioeconomic status, diet, and history of illnesses experienced by the infants indicated no important differences between the two groups. The numbers and successes of subsequent pregnancies (Table II) offer a partial answer to the occasional question whether stilbestrol treatment adversely affects fertility.

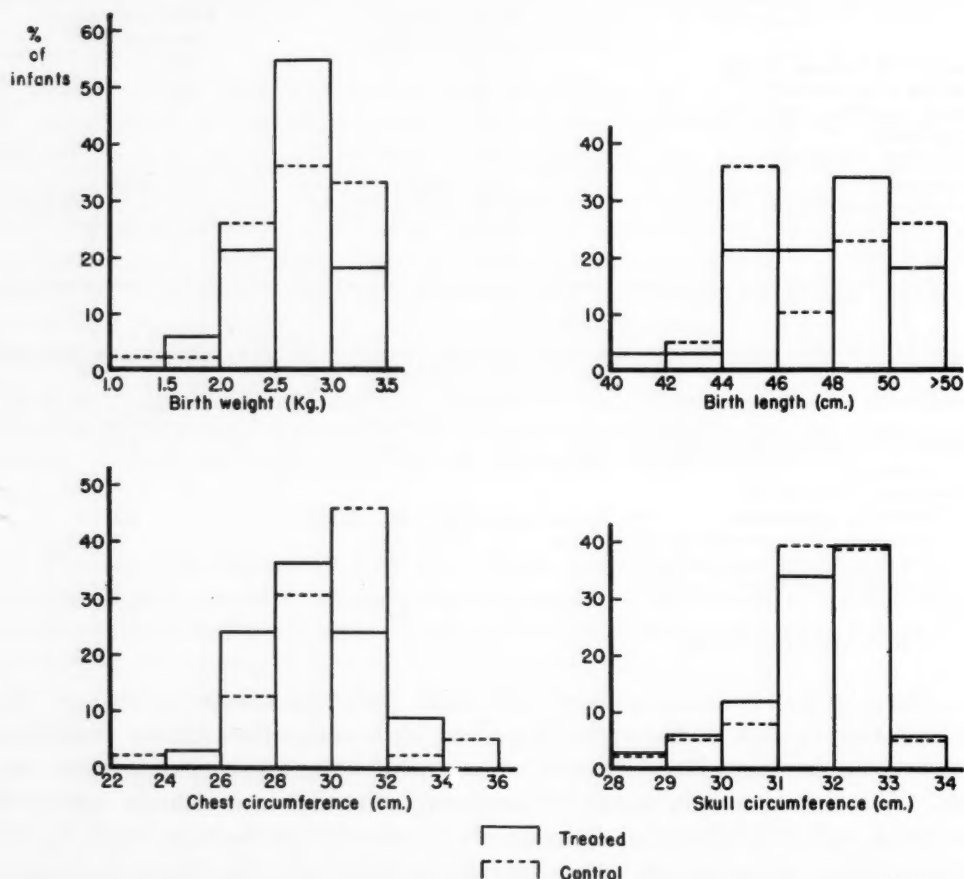


Fig. 1.—Distribution of birth weight, length, chest, and skull circumference measurements in 33 infants of stilbestrol-treated mothers and 39 infants of control mothers. The similarity of both groups of infants at birth is evident.

The difficulty of comparing infants varying both in prenatal age at birth and in postnatal age at examination was met by first comparing the birth weights, lengths, and circumferences of head and chest of all infants examined in the present investigation. As shown diagrammatically in Fig. 1, there were no significant differences at birth between the "treated" and "control" infants examined. Had it been possible to locate *all* infants originally comprising these two groups, the stilbestrol group would have shown superiority of birth weight and length<sup>4</sup> but by the chance omission of certain infants from each group,



those available for the present study were of comparable stature at birth. The postnatal growth attained in these originally similar groups was then analyzed by expressing the measurements at follow-up examination as percentiles of expected normal growth.<sup>5</sup> Although the ratings used are derived from normal full-term infants, relative success or failure of growth in prematurely born infants should nevertheless appear in such a comparison. No satisfactory standards of expected growth of premature infants are available.

The growth attained at examination from 2 to 3½ years after birth is shown in the diagrams of Fig. 2. All 4 measurements of both groups of infants tend to fall below the 50th percentile, which might be expected since the percentiles are those for infants born at term. Nevertheless, the distributions are so similar in the two groups as to indicate no significant effect of stilbestrol administration during pregnancy upon subsequent growth of resulting infants.

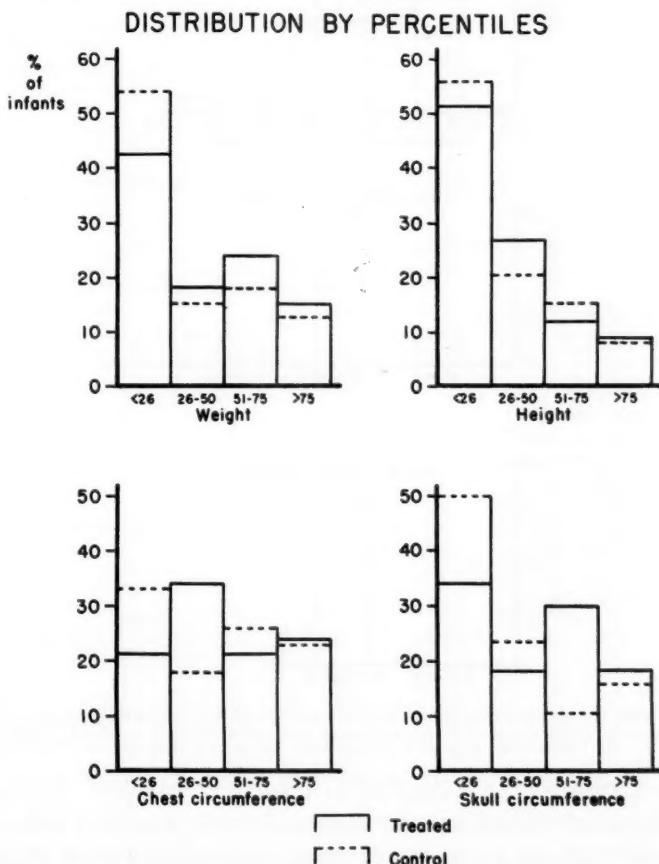


Fig. 2.—Growth attained by the infants of stilbestrol-treated and control mothers at examination 2 to 3½ years after birth. Growth of both groups of infants has been similar.

Skeletal ages attained as compared with chronological ages are shown in the upper diagram of Fig. 3. Each film was evaluated (by Dr. E. B. D. Neuhauser or Dr. M. L. Wittenborg of The Children's Hospital) in terms of number of months of skeletal age represented, and the figure divided by chrono-

logical age in months. Again, the results show no significant effect of maternal stilbestrol treatment.

Mayer and Levasseur<sup>6</sup> have reported erupted teeth at birth in 5 of 248 infants born to women treated with the synthetic estrogen, methyl bis-dehydrodoisynolic acid. Although this different estrogen was used, the observation suggested comparison of age at first dentition in infants from stilbestrol-treated mothers and controls (Table III).

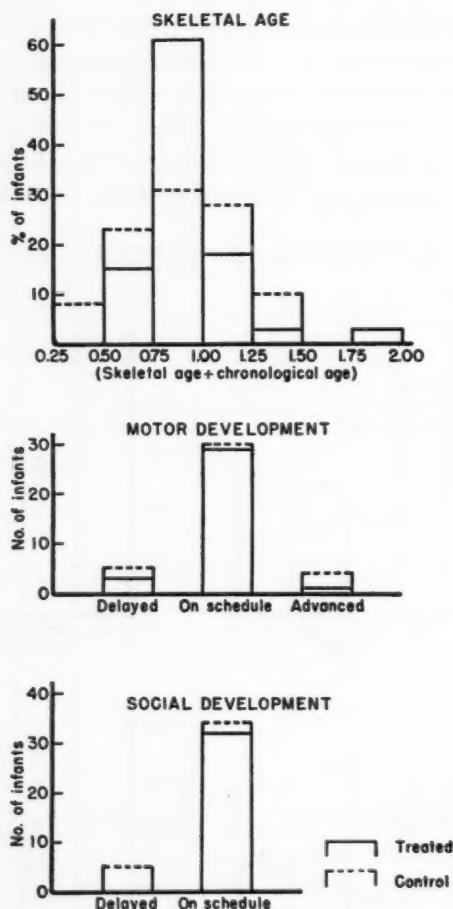


Fig. 3.—Skeletal age, motor development, and social development, attained at 2 to 3½ years by infants of stilbestrol-treated mothers versus those of control mothers.

The figures suggest no effect of stilbestrol treatment during pregnancy upon the dentition of these infants. Erupted teeth were not found at the birth of any of the 387 infants from whom these were selected for study nor in any other infants born to all other stilbestrol-treated mothers in this hospital.

The intellectual and emotional progress of the two groups of infants was assessed for us by Dr. Edith Meyer and Mrs. Harriet Hyde Sands of the Children's Medical Center, who rated each child's history of motor and social development as either on schedule, ahead of, or behind schedule. This was also done without knowledge of treatment status. Results, shown in the middle and lower diagrams of Fig. 3, do not indicate any significant differences.

One of the 33 infants whose mothers received stilbestrol was found on follow-up physical examination to have a congenital malformation, penile hypospadias. Careful search of the original hospital record revealed that this had actually been noted at birth, though the notation had escaped attention when the birth records were analyzed for the earlier paper.<sup>4</sup> No other malformations whatsoever were found by examination of the treated or control infants called back for the present study, but because this one anomaly had been missed in the preparation of the earlier paper, a careful restudy was made of the original records of all infants born to the 387 treated and 555 control mothers.<sup>4</sup>

TABLE III. AGE AT FIRST DENTITION AMONG INFANTS BORN BEFORE TERM TO WOMEN TREATED WITH STILBESTROL, AND AMONG CONTROL INFANTS

INFANTS WITH FIRST DENTITION DURING	INFANTS FROM TREATED PREGNANCIES	INFANTS FROM CONTROL PREGNANCIES
First 3 months	0	0
Fourth month	1	0
Fifth month	4	3
Sixth month	6	12
After 6 months	22	24
Total infants	33	39

The results of this analysis are shown in Table IV.

TABLE IV. CONGENITAL MALFORMATIONS

<i>I. Infants Born to 387 Stilbestrol-treated Mothers.—</i>		
A. Originally reported <sup>4</sup>	Polydactylism	1
B. Discovered on restudy of records	Hypospadias	2
Total defective infants of 387 treated mothers		3 (0.8%)
<i>II. Infants Born to 555 Control Mothers.—</i>		
A. Originally reported <sup>4</sup>	Polydactylism	2
	Meningocele	2
B. Discovered on restudy of records	Mongolism	1
	Hydrocephalus	1
	Anencephalus	1
	Hypospadias	4
	Absent hand	1
	Congenital heart disease	3
	Club feet	1
Total defective infants of 555 control mothers		16 (2.8%)

These revised data still indicate, as in the earlier paper,<sup>4</sup> no suggestion of increased frequency of congenital malformations associated with stilbestrol treatment by the routines of Smith and Smith during pregnancy.

This and the other foregoing evidences of harmlessness of stilbestrol to the human fetus deserve emphasis because of the well-known toxic effect of estrogens upon the fetuses of rodents. Relatively small dosages given to this species cause abortion or resorption of pregnancy and result in a high incidence of sex inversion in the few offspring that are carried to term.<sup>7</sup> The possibility of producing abortion or resorption of human pregnancy with estrogens has been exhaustively investigated with completely negative results. Mayer and Levasseur<sup>8</sup> report 10 malformations among 260 infants born alive

or dead after the sixth month to women who were treated with methyl-bis-dehydro-doisylnolic acid during pregnancy, an incidence of 3.8 per cent. Over half of their series of patients, however, were being treated for threatened abortion, a factor which would in itself raise the incidence of abnormal eggs.

### Summary and Conclusions

The health and growth during infancy of 33 infants born to primiparous women receiving stilbestrol during pregnancy (by the routine of Smith and Smith<sup>4</sup>) were evaluated by comparison with 39 infants of control women who received no stilbestrol. The infants selected for this study were those born before expected term—a comparison which might best bring out any subsequent differences in growth. They ranged from 2½ to 3½ years of age at the time of this study.

Histories, physical examinations, and roentgenograms showed no significant differences in the frequency of illness, the physical, skeletal, and intellectual growth, or the age at dentition, of infants and young children who had been born after maternal treatment with stilbestrol, as compared with those from control pregnancies.

The investigation led to a restudy of incidence of congenital malformations in the larger series of "stilbestrol" and control infants formerly reported.<sup>4</sup> This indicated a revised incidence rate of congenital anomalies of 0.8 per cent among the "stilbestrol" infants as compared with one of 2.8 per cent in the control infants.

It is concluded that the recommended dosage of stilbestrol during human pregnancy is without any ill effects upon the subsequent growth and development of the infant.

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## MARGINAL INSERTION OF THE CORD AND PREMATURE LABOR

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**T**HIS study is concerned with the possible role that marginal insertion of the cord may play in initiation of premature labor.

The exact causes of prematurity can be determined in only about 40 per cent of the cases.<sup>1</sup> The chief causes in order of their frequency are: (1) maternal diseases, such as toxemia, placenta previa, and abruptio placentae which necessitate premature termination of pregnancy, (2) multiple births, (3) maternal diseases with spontaneous onset of premature labor, (4) fetal monstrosities, and (5) habitual abortions. Since prematurity is responsible for about half of the neonatal deaths, it is important to know more about the etiological factors involved<sup>1</sup> in the hope of preventing or, at least, of being able to cope with its hazards, while anticipating it. For an understanding of the causes of premature labor one must have a basic knowledge of the principles underlying the onset of normal, full-term labor.

While many theories have been advanced to explain the onset of labor the actual cause of this phenomenon still remains unknown. It is generally agreed that the process of labor is initiated not by one single factor, but that many factors are involved. Among these, according to Reynolds,<sup>2</sup> are structural, humoral, nervous, nutritional, and circulatory changes taking place in the uterus, placenta, and fetus. Briefly, the uterine musculature is stimulated to growth hypertrophy and increased irritability by the estrogenic hormone. After conversion, the uterine muscle fibers are no longer stimulated to growth, but are subjected to mechanical stretching as a result of the rapid development of the fetus.

This stretching further increases the irritability of the myometrial fibers. As pregnancy progresses the myometrial and elastic tissues are subjected to ever-increasing stretching and distention, rendering the uterus highly irritable, contractile, as well as partly ischemic. This contractility, however, is inhibited by the presence of progesterone. The two hormones, estrogen and progesterone, are supplied in the human species by the ovaries (corpus luteum of pregnancy) during the first trimester of pregnancy and by the placenta thereafter.

At about the beginning of the eighth lunar month the placenta undergoes gradual and progressive changes. Thrombosis occurs in many of the venous sinuses of the placenta and the lumina of many of the blood vessels become more or less obstructed by giant cells. It is further known that before the onset of labor the hormones which tend to stabilize the pregnancy are withdrawn from circulation. Active uterine contractions follow soon after this withdrawal and labor is initiated.

TABLE I. PERTINENT INFORMATION ON 22 CASES OF MARGINAL INSERTION OF THE CORD ASSOCIATED WITH PREMATURE LABOR

PATIENT	PREMA- TURITY IN WKS.	MEMBRANES RUPTURED PREMA- TURELY	VAGINAL BLEEDING	FETAL DISTRESS	INSERTION OF CORD	PARA	GRAVIDA	WEIGHT OF BABY		REMARKS
								POUNDS	OUNCES	
R. T.	2	Yes		Yes	1 cm. from margin	0	2	7	14	
A. M.	3	Yes			Marginal	0	1	6	6	
F. I.	2	Yes		Yes	1 cm. from margin	0	2	6	14	
G. R.	2½	Yes			Battledore	1	3	6	4	
S. I.	2½	Yes			Battledore	0	1	6	12	
A. R.	3	No			Battledore	0	1	6	6	
F. S.	3½	No		Yes	Battledore	0	1	5	2	Stillborn, not macerated
C. S.	8	No	Moderate	Yes	1 cm. from margin	0	1	4	5	
Z. M.	3½	Yes		Yes	1 cm. from margin	1	2	5	9	
N. H.	3	Yes		Yes	1 cm. from margin	1	2	5	5	
G. V.	4	Yes			Velamentous	1	2	6	4	
G. C.	2½	Yes			1 cm. from margin	2	3	6	2	
M. P.	5	Yes		Yes	Marginal	0	1	4	8	
W. C.	3	Yes		Yes	1 cm. from margin	0	1	5	14	
L. B.	6	No		Yes	Battledore	0	2	4	3	
F. F.	4	No		Yes	Battledore	0	1	4	10	
W. A.	4	Yes	Profuse	Yes	Velamentous	0	2	3	14	Cesarean section, bleeding into cord, retroplacental clot
L. R.	3	Yes			Battledore	0	1	5		
A. S.	6	Yes	Profuse		Marginal	1	2	4	12	Low implantation of the placenta
M. E.	6	No	Moderate	Yes	Velamentous	1	2	5	6	Bleeding into cord, partial premature separation
L. L.	4	No	Moderate	Yes	Battledore	0	1	5	1	Bleeding into cord, partial premature separation
E. S.	2½	Yes			Battledore	0	1	6	2	

As has already been stated, the specific causes leading to the initiation of this process are, as yet, unknown. All that can be stated at present is that a definite relationship exists between the uterus, placenta, and fetus by which a balance of opposing forces is maintained until the period of fetal ripening, at which time the inhibiting forces are withdrawn, the balance disturbed, and the uterus begins to expel the ripe fetus. When we speak of "ripening" we imply that a point is reached in the development of the fetus when its nutritional supply in the uterus becomes inadequate and the pregnancy is consequently terminated. It has been established that some abnormality in any of the three main factors concerned with the maintenance of the pregnancy, the uterus, the placenta, or the fetus, may cause early or premature labor.

Thus, the uterine musculature may, under certain conditions, become overstretched and excessively irritable to such a degree that labor may be initiated prematurely. This is true in cases of multiple pregnancy, as well as in cases of hydramnios. In the latter instance, acute hydramnios usually terminates before the sixth month,<sup>3</sup> while in the chronic variety, premature labor is frequent.<sup>1</sup> Premature labor is also frequent in cases of fibroids of the uterus due to overstretching of parts of the uterine musculature. The same is true of hypogonadal uteri where rapid growth of the fetus causes an overdistention of the underdeveloped muscle fibers of the uterus and premature labor ensues.

As far as the placenta is concerned, it is well known that premature separation of the placenta is frequently followed by an early onset of labor. According to Greenhill,<sup>1</sup> the slight hemorrhage under the placenta will frequently activate the uterus into vigorous action. This prevents intrauterine bleeding and causes the child, often alive, to be delivered quickly. In cases of more advanced abruptio placentae labor may be sudden, the contraction of the uterus may be strong, the external os dilates quickly, and the case may terminate spontaneously.

As to the fetus, it has long been observed that monsters are very frequently delivered prematurely.<sup>1</sup> The same is true of malformations. Potter,<sup>4</sup> in a post-mortem study of 503 premature and "previable" infants, found that 10 per cent had malformations. Stevenson, Worcester, and Rice,<sup>5</sup> in a study of congenitally malformed infants, found that the incidence of prematurity was greater in their series than in a control series.

From our observations reported here it would appear that battledore placenta may sometimes be responsible for the premature initiation of labor. It is postulated that in cases of marginal insertion of the cord there may, under certain conditions, occur an interference with fetal circulation. This may result in fetal embarrassment and upset the balance of opposing forces existing between the uterus, placenta, and fetus for the maintenance of pregnancy. The disturbance of this balance may bring on labor prematurely.

### Material

In a series of 512 consecutive deliveries, each placenta was examined for the site of the insertion of the cord. The cord was considered inserted marginally in the placenta if it was implanted at its very margin or not further than 1.5 cm. away from it. Thirty-two patients were found to have battledore pla-

TABLE II. PERTINENT INFORMATION ON 10 CASES OF MARGINAL INSERTION OF THE  
CORD ASSOCIATED WITH FULL-TERM LABOR

PATIENT	PERIOD OF GESTATION (WEEKS)	MEMBRANES RUPTURED PREMATURELY	VAGINAL BLEEDING	FETAL DISTRESS	INSERTION OF CORD	PARA	GRAVIDA	WEIGHT OF BABY		REMARKS
								POUNDS	OUNCES	
S. K.	40	Yes		No	1 cm. from margin	2	1	7	2	
L. F.	39	No		No	Marginal	3	2	6	15	
M. N.	40	Yes		No	Marginal	3	2	7		
A. P.	40	Yes		No	Battledore	4	2	6	10	
O. T.	39	Yes	Profuse	Yes	1 cm. from margin	0	1	7	1	Cesarean section, marginal placenta previa
K. L.	41	No		No	Marginal	0	2	6	14	
M. L.	40	Yes		No	Battledore	3	2	7	6	
S. T.	40	Yes		No	Marginal	4	3	7	3	
W. G.	40	No		No	1 cm. from margin	0	2	7	4	
K. H.	40	No		No	Marginal	0	1	7	6	



centas (Tables I and II). Of these, 22 patients (68 per cent) went into labor prematurely. Labor was frequently preceded by rupture of the membranes. None of these patients had any systemic diseases, signs or symptoms of toxemia, abruptio placentae, multiplicity, or hydramnios to account for the early onset of labor. There were no instances of monstrosity or malformation in the infants delivered in this group. The one significant finding was a marginal insertion of the cord.

As can be seen from Table I, the deliveries occurred three to eight weeks prior to the expected date of confinement. Ten of the infants were in distress during labor, necessitating prompt interference in some of the cases. Two infants died during labor. A few cases are of sufficient interest to warrant a more detailed account.

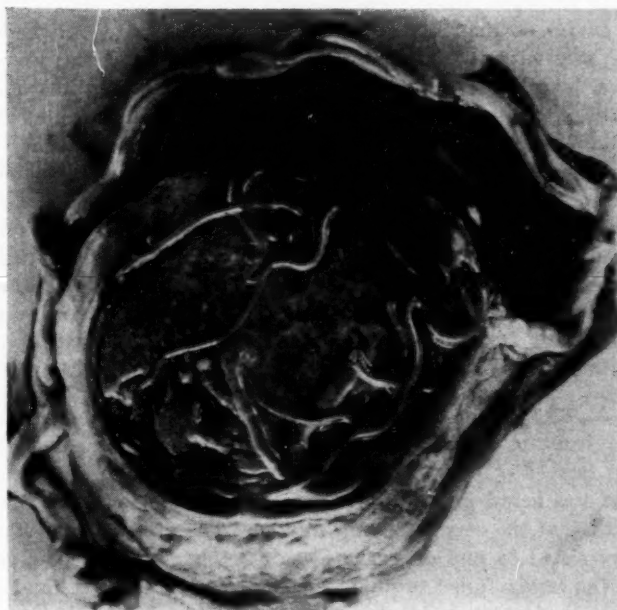


Fig. 1.—Placenta from Case 2 showing marginal insertion of the cord.

### Case Reports

CASE 1.—A. R., a 26-year-old white woman, gravida i, para 0, was admitted to the hospital on April 20, 1952, with ruptured membranes for the previous twenty hours. The expected date of confinement was May 12, 1952. The prenatal course was uneventful. Rectal examination revealed a vertex presentation in right occipitoanterior position. The station was minus one. The fetal heart was heard in the right lower quadrant, with the rate of 140 a minute. The cervix was two fingers dilated, the pains occurring every seven to eight minutes. There was no vaginal bleeding, but a heavy bloody show was present. Labor pains began four hours prior to admission. During the course of the next few hours good progress was made, but it was noted that the fetal heart tones were rapid, 160 to 170 per minute. Seven hours after admission the patient was delivered with low forceps under saddle block anesthesia. The baby was resuscitated after several minutes and left the delivery room in good condition. He weighed 6 pounds, 6 ounces. The placenta showed a marginal insertion of the cord. The important features in this case were the premature onset of labor, preceded by ruptured membranes and the fetal embarrassment as shown by the fetal heart rate during labor and the requirement of resuscitation after delivery. The possible association of these findings with the marginal insertion of the cord will be discussed later.

CASE 2.—F. S., a 22-year-old white woman, gravida i, para 0, was admitted to the hospital on April 23, 1952. Labor started three hours prior to admission. Membranes were ruptured for the previous ten hours. On admission, labor pains were occurring every five minutes. The fetal heartbeat was heard in the left lower quadrant, 160 per minute. Vaginal examination revealed the cervix to be  $2\frac{1}{2}$  fingers dilated; the presenting part was a vertex at 0 station. The expected date of confinement was May 20, 1952. Two hours after admission the dilatation was  $4\frac{1}{2}$  fingers. Fetal heart sounds could no longer be heard. A short time thereafter, the patient was delivered spontaneously of a stillborn male infant, not macerated. The only positive finding was a marginal insertion of the cord (Fig. 1). The weight of the baby was 5 pounds, 2 ounces.

CASE 3.—A 28-year-old gravida ii, para i, was admitted to the hospital on Oct. 11, 1952, because of pains in the right lower quadrant associated with vaginal bleeding for the past ten hours. The expected date of confinement was Nov. 25, 1952. The prenatal course, to date, was uneventful. Abdominally, there was a painful area in the right lower quadrant. There were intermittent irregular uterine contractions. The uterus was somewhat hard, but not of a boardlike consistency. The fetal heart was heard in the lower left quadrant at the rate of 150 per minute. A cystogram was made to rule out placenta previa. The patient complained of increasing pains in the right lower quadrant. The diagnosis of premature partial separation of the placenta was made and it was decided to rupture the membranes and induce labor with intravenous Pitocin. This was done and three hours after rupture of membranes the patient was delivered with low forceps of a living female infant who weighed 5 pounds, 6 ounces. The pathological report of the placenta showed a marginal insertion of the cord with bleeding into the cord and a retroplacental blood clot occupying about one-third of the placental surface. The primary pathology in this case was the hemorrhage into the cord caused, most probably, by its marginal insertion. The retroplacental hemorrhage was secondary to the bleeding into the cord.

CASE 4.—W. A., 36 years of age, gravida i, para 0, was admitted to the hospital on Aug. 21, 1952, because of rupture of the membranes and irregular labor pains. The expected date of confinement was Sept. 15, 1952. The uterus was the size of an eight months' pregnancy. The fetal heartbeat was heard in the right lower quadrant and was of good quality. Rectal examination revealed that the cervix was not dilated. The presenting part was high at minus 2 station. Pains persisted on and off every seven to eight minutes. The patient was making little progress and the cervix failed to dilate. She was given sedatives and general supportive treatment. At 4 P.M. the patient suddenly had a gush of blood from the vagina. The bleeding continued, but was not very active. The general condition of the patient remained the same. The fetal heartbeat became very rapid, 188 per minute and distant. The baby was apparently in distress and immediate delivery was indicated. Since the cervix was still 2 cm. dilated and the presenting part high, delivery by cesarean section was performed. A premature stillborn infant was delivered. The birth weight was 3 pounds, 4 ounces. The placenta was situated on the posterior wall of the uterus near the fundus. The cord had a velamentous insertion arising from the membranes about 1 cm. away from the margin. There was bleeding into the cord and a retroplacental clot on the part of the placenta adjacent to the cord. In this case labor was premature, preceded by rupture of the membranes due to the velamentous insertion of the cord. There was hemorrhage in the cord with retroplacental clot which resulted in the fetal death in spite of the prompt delivery of the baby at the first sign of uterine bleeding.

CASE 5.—A. S., a 25-year-old white woman, was admitted to the hospital on Oct. 7, 1952, because of profuse vaginal bleeding. The patient was a gravid ii, para i. The expected date of confinement was Nov. 20, 1952. The patient stained and bled on and off throughout pregnancy. On the day of admission she bled profusely. She had no labor pains and was ordered to the hospital. Upon admission there was no active vaginal bleeding. Her general condition was good. The blood pressure was 112/80. The fundus was the size of a seven months' gestation. The fetal heartbeat was of good quality, the fetus was of

fair size in breech presentation. No rectal or vaginal examinations were attempted. Because of the patient's favorable condition no interference was contemplated. Three hours after admission the patient went into labor. The membranes ruptured shortly after. The cervix was fully dilated after two and one-half hours of labor. A male infant was born by assisted breech delivery. His birth weight was 4 pounds, 2 ounces, and he was in good condition. The placenta was implanted low in the uterus. The maternal side was deeply cyanotic. The cord was inserted at the very margin of the placenta. While the bleeding, in this case, may have been due chiefly to the low implantation of the placenta, we feel that the marginal insertion of the cord was the main contributing factor in initiating labor prematurely.

### Comment

While the number of cases in this report is insufficient to lead to any definite conclusions, the association of marginal insertion of the cord with premature labor and early rupture of the membranes was frequent enough (65 per cent) to preclude the possibility of mere coincidence.

The physiological basis for this phenomenon may lie in the possibility that, under certain unfavorable conditions, the marginally inserted cord may bring about some interference with the blood supply to the fetus. This may cause an inadequate supply of nourishment to the fetus, the balance existing between the uterus, placenta, and the fetus may be disturbed, and labor initiated.

That marginal insertion of the cord may affect the development and growth of the fetus was suggested by one of us<sup>6</sup> in a study of the variation in size and weight of twins. According to Reynolds,<sup>7</sup> growth and maturation of the fetus after conversion of the uterus depend, to an important degree, upon the condition of circulation of maternal and fetal bloods, respectively, through the organ of exchange, the placenta. He further states that the pressure at term on the placental vascular bed reduces the amount of nutriment available to the fetus, thus modifying its further growth. The thinned-out peripheral portion of the placenta may be compressed more easily than its thicker portion. When the cord is inserted marginally and in the lower pole of the uterine cavity, it is conceivable that the vessels of the cord, as well as the adjacent portion of the placenta, may become compressed to a degree sufficient to interfere with the adequate blood supply of the fetus. This will cause fetal embarrassment and affect the balance which exists between the uterus, placenta, and fetus, resulting in early initiation of labor. Furthermore, marginal insertion of the cord is responsible for some complications during labor. The cord may become sufficiently compressed to stop the flow of blood through it completely, thus causing intrauterine death of the fetus. This was illustrated in the first case report in this series. Then again, the vessels of the cord may rupture, causing vaginal bleeding during labor, and sometimes resulting in fetal death. Two of our cases had this complication. That this is not a rare occurrence is substantiated by Donnelly<sup>8</sup> who reported eight cases of battledore placenta and one of circumvallate, in which some degree of bleeding occurred during pregnancy or labor. Some of these cases were mistakenly diagnosed as placenta previa. Cesarean sections were performed in two of these cases.

From the clinical point of view the observation made in this report may have some significance. The possibility of marginal insertion of the cord should be borne in mind in any case of premature labor and early rupture of the membranes when the patient has no systemic disease, no sign or symptom of toxemia, and no evidence of cephalopelvic disproportion, malposition, or multiplicity. The fetal heart should be watched constantly in a case of this sort, since the fetus may become distressed at any time during labor due to interference with the circulation. Similarly, one should be on the lookout for any bleeding dur-

ing labor. This may signify rupture of the cord vessels with retroplacental hemorrhage, in which case the fetus may show signs of embarrassment and prompt delivery may become indicated.

### Summary

1. The present-day concepts of the causes of onset of premature labor and labor at term are reviewed.
2. In a series of 512 consecutive cases, 32 cases of marginal insertion of the cord were observed.
3. Of these, 22 cases, or 65 per cent, were associated with premature onset of labor which was frequently preceded by rupture of membranes.
4. Fetal distress was a frequent finding in the 22 cases cited and in 2 instances there was vaginal bleeding during labor.
5. It is suggested that marginal insertion of the cord may cause interference with adequate fetal circulation and impede the nutrition of the fetus and thus initiate labor prematurely.

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## **A THIRTY-SEVEN-YEAR SURVEY OF ECTOPIC PREGNANCY\***

### **266 Consecutive Cases Without Mortality**

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**F**ROM 1915 to date 266 consecutive cases of extrauterine pregnancy were admitted to the Southern Division of the Albert Einstein Medical Center.† The first 40 cases in this series were reported in 1929. In 1947 an additional 172 cases were analyzed and reported. Since our last report 54 cases were admitted and treated. Each of these 266 cases were treated by operation and all recovered.

The purpose of this report is twofold: to bring our survey up to date and to evaluate the recent downward trend of mortality rates.

It has been said that inconsistency is the only constant factor in ectopic pregnancy. Its clinical entity is atypical. The voluminous statistical data and mortality rates are variable and at times confusing. Mortality rates range from zero to 12 per cent.

Several noteworthy series, each over 100 cases without mortality, are recorded. In 1928 Sellers and Sanders reported 211 cases, Echols reported 103 cases in 1934, and in 1938 Bethel Solomons reported 214 cases. More recently in 1944 J. R. Miller, in discussing the report of the Philadelphia Maternal Mortality Committee, stated that "at the St. Francis Hospital in Hartford, Connecticut, 141 cases were treated since 1929 without mortality."

### **Study of Mortality Trends**

Our aim is to evaluate mortality statistics only in so far as they indicate mortality trends. For the sake of clarity, statistics will be divided into three chronological epochs, the first antedating the work and contributions of Lawson Tait in 1883, the next covering a span of 57 years, from 1883 to 1940, and the third from 1940 to date.

In 1876 Parry collected 500 cases from the literature. Of this number 366 patients died, a mortality rate of 73 per cent.

In 1883 Lawson Tait was the first to operate on a previously diagnosed case of ruptured ectopic pregnancy. The patient died. Of his next 40 operations, none died. By 1891, eight years after this pioneer work, Schauta demonstrated that prompt operation reduced the previous appalling mortality rate of 73 per cent to 5.6 per cent. This rate remained practically stationary for 57 years. This is clearly shown in Gordon's noteworthy analysis in 1936 wherein he reviewed 3,343 cases collected from 15 different sources, each over 100 cases. The over-all mortality rate was 4.6 per cent.

\*Presented at a meeting of the Obstetrical Society of Philadelphia, Nov. 6, 1952.

†Formerly The Mount Sinai Hospital.

Since 1940 there has been a definite downward trend in mortality rates. The year 1940 is selected arbitrarily since we are too close to this epoch to be able to evaluate the exact time of change. A number of factors influencing this change occurred about this time, some of which are: improved educational standards, introduction of chemotherapy and antibiotics, freer access to blood for transfusion, the discovery of the Rh factor, and improved anesthesia. These did not all appear at the same time. The complete impact of their influence cannot be evaluated until more time has elapsed. Many statistical reports in the literature show this downward trend. The recent report of Beacham and Collins of New Orleans best exemplifies it. At the Charity Hospital they report a consistent mortality rate ranging between 11 and 12 per cent in the years 1920 to 1937. In 1937, after overcoming some factors and improving others, all of which were local in character, they reduced the mortality rate to 2.7 per cent. This was further reduced to 1.7 per cent between 1945 and 1948.

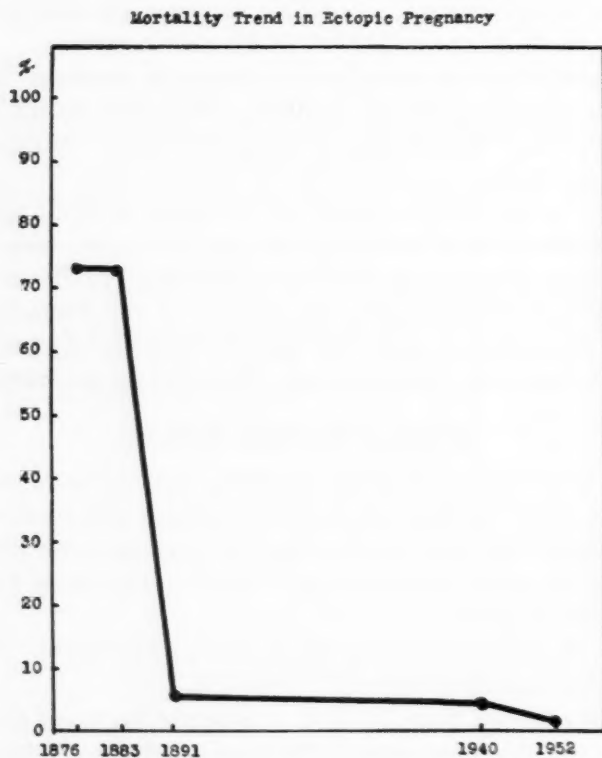


Fig. 1.

Borrowing the statistical methods used by Gordon, we surveyed the mortality rates reported from 1944 to date, as shown in Table I.

Fourteen different sources supplied 3,402 cases, none under 100. Of these 66 patients died, a mortality rate of 1.95 per cent.

It is interesting to note that the last available United States Vital Statistics in 1949 reports 203 maternal deaths due to ectopic pregnancy as against 3,559,529 live births. The ratio of extrauterine pregnancies to live births has

been variously estimated from Schumann's figure of 1:300 down to 1:105. Both the Federal Vital Statistics of 203 ectopic deaths and Schumann's ratio of 1:300 are open to controversy. However, on the basis of these figures we get a mortality rate of 1.7 per cent in the United States for the year 1949. This figure is close to the 1.95 per cent calculated on the basis of our analysis of 3,402 cases.

TABLE I. MORTALITY SURVEY, 1944-1952

SOURCE	YEAR	CASES	DEATHS	PER- CENTAGE
Miller, J. R. <sup>16</sup>				
Hartford Hospital	1944	184	2	0.9
St. Francis Hospital	1944	141	0	0
Siegler, S. L. <sup>24</sup>	1945	127	5	3.9
Marchetti, A. A., Kuder, K., and Kuder, A. <sup>15</sup>	1946	141	1	0.7
MacFarlane, K. T., and Sparling, B. W. <sup>14</sup>	1946	110	3	2.72
Nucci, R. Charles <sup>17</sup>	1946	150	4	2.6
Jarcho, J. <sup>12</sup>	1947	173	5	2.9
Danforth, W. C. <sup>6</sup>	1947	174	4	2.29
Beacham, W. D., Collins, C. G., Thomas, E. P., and Beacham, D. W. <sup>2</sup>	1948	131	4	2.89
Davidson, H. B., and Mandelbaum, C. C. <sup>7</sup>	1950	258	14	5.8
Henderson, D. N., and Bean, J. L. M. <sup>11</sup>	1950	302	7	2.3
Anderson, G. W. (Baltimore City) <sup>1</sup>	1951	862	14	1.6
Douglas, F. D., and Douglas, G. C. <sup>8</sup>	1951	256	2	0.78
Campbell, R. M. <sup>4</sup> (4 Seattle Hospitals)	1952	393	1	0.25
Total		3,402	66	1.95

Neither time nor space will permit a profound evaluation of the factors influencing the present downward trend of mortality rates in ectopic pregnancy. The following is a brief résumé of some of these factors in correlation with our experience.

*Diagnosis as a factor:* A correct diagnosis was made in 90 per cent of our cases analyzed. After corrections were made for errors in diagnosis, later proved to be a different condition, the percentage dropped to 56 per cent. This is comparable to reported statistics; e.g., Scheffey and Farell report 78.7 per cent correct preoperative diagnosis, Campbell 81 per cent, Urdan 58 per cent, Marchetti 90 per cent preoperative and 52 per cent corrected, Bell and Ingersoll 67.6 per cent preoperative and 52 per cent corrected.

Correct preoperative diagnosis is only a relatively important factor. On four occasions we failed to make a correct diagnosis in patients who were admitted in shock, but shock was instantly diagnosed and combated. These recovered. One of the four was well enough to go home with an undiagnosed ectopic pregnancy. She returned in six months, at which time the diagnosis was again missed. Her preoperative diagnosis was uterine fibroid and the findings at operation were an old ruptured ectopic pregnancy with an organized blood clot adherent to the uterus.

*Blood transfusion:* The Philadelphia report and other studies made on fatalities justly condemn the inadequate use of blood. This shortcoming is rapidly being overcome since the advent of blood banks. Campbell reports that in the last six years his patients received an average of 2.1 units of blood.

In 1947 we reported an average of 1.8 units of blood administered to 45 patients admitted in a state of shock. In our present series of 54 cases, 7 were in shock. They received an average of 2.5 units of blood.

In cases of shock, the sense of impending tragedy is often relieved by the knowledge that blood is available. Previous to the installation of a blood bank at our institution, a group of professional donors residing close to the hospital was organized. These were available on short notice. On several occasions during this period, when a donor was not at hand, the surgeon gave a pint of his blood and then proceeded to operate.

Blood is vital. However, Solomons' 214 patients, 37 of whom were in shock, survived without the use of blood. He emphasized, however, the importance of the immediate recognition of shock and urged adequate measures to combat it. This is in line with our conclusion in the 1947 report that "the greatest single factor in reducing the mortality rate of ectopic pregnancy is early recognition of shock and its immediate treatment."

*The social-economic factor:* In the past considerable emphasis has been placed on what may loosely be termed the social-economic factor. The United States Bureau of Vital Statistics groups maternal mortality rates into white and nonwhite. The rate is almost twice as high in the latter group. Likewise, there are numerous statistics showing a higher ratio of cases in the nonwhite group of patients with ectopic pregnancy admitted in shock. These facts suggest that there exists an element of contributory negligence on the part of the patient in the poorer segment of the population. The question of the importance of this factor in hospital mortality statistics is debatable. Since there was only one nonwhite patient in our first 212 cases analyzed, we cannot, on the basis of our experience, comment on the racial factor. The division of cases into ward and private is a fair criterion of the social-economic factor. Of 54 cases admitted since 1946, 25 were ward patients treated by the resident. There is little doubt that the social-economic factor has considerable bearing on national maternal mortality rates. What, if any, influence it has on hospital mortality rates in ectopic pregnancy is questionable. Some of the most notable drops in mortality rates that have been recently reported are from sources serving large groups of nonwhite patients. Charity Hospital of New Orleans reports a drop from 12.3 per cent to 1.7 per cent. Baltimore City statistics as reported by Anderson from 1944 to 1948 show an over-all mortality rate of only 1.6 per cent.

We have attempted to emphasize the fact that fatalities in ectopic pregnancy, by and large, are due to irreversible shock. Patients are frequently brought to the hospital in a state of shock, but it must be a rare occasion that on admission shock is irreversible. We suggest that once a patient is admitted to a hospital, her death is the institution's responsibility. Of course contributory factors cannot be erased entirely from the calculations.

### Conclusions

In a subject as bizarre as ectopic pregnancy, to draw conclusions is difficult; to draw none is evasive. Dogmatism is risky. With this risk in mind, we first conclude that one may, on occasion, err in diagnosis, in surgical judg-



ment, or surgical technique without losing the patient, but delay in combating shock is fatal.

Our second conclusion is that the time is rapidly approaching when the present falling mortality rate of ectopic pregnancy will reach the low general level now existing in pelvic surgery exclusive of malignancy.

### Summary

1. Two hundred sixty-six consecutive cases of ectopic pregnancy without mortality have been reported.
2. The trend in mortality rates in ectopic pregnancy was reviewed.
3. Conclusions were drawn.

Finally, we feel impelled to quote the closing remark of our 1947 report: "That we did not have a single death due to embolism or other so-called unavoidable complications, we credit to good fortune."

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### Discussion

DR. DAVID M. FARELL.—A series of 266 consecutive cases of ectopic pregnancy extending over a period of 37 years, without a fatality, is indeed an enviable record. Their success I am sure is due to good diagnosis, and prompt and proper treatment.

That the mortality rate in ectopic pregnancy is being reduced is apparent to all. Since 1921, 277 cases of ectopic pregnancy have been admitted to the Gynecological Ward of the Jefferson Medical College Hospital. Dividing these admissions into three 10 year

periods, we find that during the first period, 1921 to 1931, 75 cases were treated with a mortality rate of 4.8 per cent. During the second period, 1931 to 1941, 87 cases were treated with a mortality rate of 1.3 per cent, and during the third period, 1941 to 1952, 122 cases were seen with a mortality rate of 0.8 per cent.

I agree with Dr. Leff that improved methods of combating blood loss, treatment of shock, and improved means of anesthesia have all contributed to the decrease in the mortality rate. Thus in our first series (1921-1931), two patients died in shock before being operated upon. With our present methods of blood replacement and treatment of shock these patients might have been saved.

However, I cannot agree with the essayist's statement that "diagnosis is only a relatively important factor." One has to be indeed fortunate to have a patient admitted in shock, as reported in this series, for her to go home without a correct diagnosis and return at a later date, when, at operation, an old ruptured ectopic pregnancy was found. One does not often get a chance at a second guess in a ruptured ectopic pregnancy. Surely, the earlier the diagnosis, and the sooner surgery is performed the less need there will be for the heroic measures needed to combat blood loss and shock.

The statistics at Jefferson Hospital bear out this fact, in that the finding of intact tubal pregnancy, indicating earlier diagnosis, has risen from 14 per cent in the first period (1921-1931) to 21 per cent in the 1941 to 1951 period, this being in inverse ratio to the mortality rate.

It would be interesting to know how many of the patients who were admitted in shock, as noted in the paper, were operated upon, and had other pathology than ectopic pregnancy, and the ultimate results in these cases.

It is noteworthy that in the author's first 212 cases there was only one nonwhite patient. Williams and Corbitt in analyzing 2,204 ectopic gestations in Philadelphia from 1931 to 1943 noted a mortality rate of 4.6 per cent with the ratio twice as high in the Negro race. Anderson of Johns Hopkins noted a similar ratio in their series. They suggest that this increased frequency of ectopic gestations in the Negro race may be due to the increased incidence of pelvic inflammatory disease. In the Jefferson series, 40 per cent of our patients showed evidence of pelvic inflammatory disease, and 26 per cent had previous abdominal operations. This high incidence of inflammatory disease and the role that postoperative adhesions may play in causing mechanical hindrance in the tubes may be an important etiological factor in the production of an ectopic gestation.

DR. ARTHUR FIRST.—Was there any incidental surgery done and if so, how much effect did this have on the morbidity? How many of these patients went on to a later normal pregnancy and how many went on to repeat ectopic pregnancies? I think this information would be especially valuable for those interested in the problem of fertility and sterility. May I emphasize the importance of a careful study of the remaining tube in women who have suffered one ectopic pregnancy before allowing another pregnancy to occur.

DR. LEFF (Closing).—We do not maintain that correct preoperative diagnosis in ectopic pregnancy is not a very important factor, but we do believe that it is only a relatively important factor as a cause of death. The fact remains that the percentage of failures in correct preoperative diagnosis of ectopic pregnancy is fairly high. It averages between 10 per cent and 40 per cent. We emphasize the importance of immediate recognition and treatment of shock. In relation to this factor, correct preoperative diagnosis is only relatively important.

As to the racial and economic factor as a cause of death, there is no doubt that statistics point to the fact that the mortality rate is much higher in the nonwhite group. However, we cannot escape the fact that the best improvement in mortality rates came out of Baltimore and New Orleans. Their mortality rates now compare favorably with those of clinics treating a preponderantly white group.

In answer to Dr. First, 25 per cent of this series had incidental surgery. I regret that I do not have the information on the number of patients in the series who subsequently had either ectopic or normal pregnancies.

## **PREGNANCY FOLLOWING MAJOR THORACIC SURGERY FOR TUBERCULOSIS\***

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THE employment of major thoracic surgery in the management of extensive unilateral pulmonary tuberculosis has increased greatly in recent years. The ready availability of multiple antibiotics, improved anesthetic methods, blood transfusions, metabolic drugs, and newer means in physical therapy have contributed to the steady shift of emphasis toward the surgical management of tuberculosis wherein one lung exhibits cavitation, ulcerative lesions, or a widespread diseased process. Segmental or total lung resection, three-stage thoracoplasty and cavernostomy are no longer surgical rarities in tuberculosis treatment. While these procedures are formidable in themselves they do offer in selected cases a greater hope than the slower collapse methods to restore these tubercular women to their home and family life. It is for these same reasons that the obstetrician and phthisiologist should review the reproductive status of these surgically salvaged tubercular women. Together they can provide clinical judgment for the woman and her husband on the difficult decision whether subsequent pregnancies shall be permitted or interdicted. In the clarification of joint judgment it is logical we should review the experience of others and ourselves to arrive at a sounder factual basis in support of these opinions.

Manifold articles, texts, and symposia have been concerned with the effects of tuberculosis upon pregnancy or pregnancy upon the tuberculous case. The present-day consensus that pregnancy has no deleterious effect upon pulmonary tuberculosis has many ardent supporters.<sup>1-24</sup> Today there are but relatively few dissenting opinions.<sup>25-35</sup> This evidence gains added credence by the increased number of authors who state that the interruption of pregnancy is rarely, if ever, indicated.<sup>5, 16, 19, 22, 23, 33, 36-40</sup> There are numerous writers who indicate that the interruption of pregnancy is especially more harmful if performed after the first trimester<sup>5, 12, 15, 17, 19, 24, 25, 32, 33, 40-47</sup> and other authors are even more positive and state unequivocally that the interruption of pregnancy can be more harmful than term delivery.<sup>22, 41-45</sup>

Cohen,<sup>17, 20</sup> Friedman and Garber,<sup>19</sup> Schaefer,<sup>47</sup> and Johnson and his co-workers<sup>33</sup> have written extensive valuable monographic articles upon the foregoing problems. It is not our purpose to allude to these general propositions. Since it appears well established that the pregnant tubercular patient does as

\*Read at a meeting of the New York Obstetrical Society, Dec. 9, 1952.

well as or better than her nonpregnant sister<sup>3, 9, 11, 13</sup> we were interested in determining whether the additional factor of prior or concurrent thoracic surgery for pulmonary tuberculosis alters the obstetric situation. We also sought to learn if variables existed between the pregnancy and maternal outcome and the various types of major chest surgery.

It has been 45 years since the first modern thoracoplasty was performed in 1907 by Friedrich<sup>48</sup> at Bauer's suggestion. Heidenhain<sup>49</sup> is usually credited for doing the first successful lobectomy in 1901. Graham<sup>50</sup> in this country in 1933 was the first to do a successful one-stage pneumonectomy. In the past twenty-eight years there has been an increasing number of case reports of thoracoplasty prior to or during pregnancy. It is unfortunate that these studies range from a few well-documented articles to many others which mention in only a few lines their follow-up observations about the outcome of pregnancy or the effect of repeated pregnancies upon the tuberculous process for which the patients underwent operations.

Thoracoplasty was first performed during pregnancy in 1924 by Saye.<sup>51</sup> The first to report about pregnancy following thoracoplasty was F. Jessen<sup>52</sup> in 1929. Since these dates we have been able to collect from the world literature 119 cases wherein thoracoplasty was performed during pregnancy or pregnancies followed this type of surgery. Thirty-four of these patients were operated upon during their pregnancies<sup>51, 64, 66, 70-76</sup> and 85 additional patients were noted to have ninety-eight pregnancies subsequent to their thoracoplasties.<sup>14, 16, 37, 52-69</sup> The limited analysis of this experience is summarized in Table I.

TABLE I. WORLD LITERATURE, 1924 TO 1952

TYPE OF SURGERY	PREGNANCY OUTCOME				MATERNAL OUTCOME		
	ABORTIONS		PRE-MATURE BIRTH	TERM BIRTH	DEAD	LIVING	
	SPONTANEOUS	THERAPEUTIC				ACTIVE DISEASE	NO APPARENT ACTIVE DISEASE
Lobectomy or Pneumonectomy							
During				2			2
Before				6			6
Thoracoplasty							
During				34	1	1	32
Before	3	2	8	85	4	7	74
Total	3	2	8	127	5	8	114

In the world literature we have been able to collect only one case of pneumonectomy performed during pregnancy. Thompson and Bressler of the New York Medical College performed the first pneumonectomy upon a pregnant woman<sup>77</sup> in 1949 at the Metropolitan Hospital. This case is included in our study. Schaefer and Epstein<sup>78</sup> reported one case of lobectomy during pregnancy. Six additional cases of pregnancy subsequent to lobectomy or pneumonectomy for tuberculosis have also been noted.<sup>79</sup>



### Material

From the records of the Metropolitan Hospital we have been able to assemble data upon a series of 25 women who submitted to major thoracic surgery during pregnancy or who became pregnant following extensive chest surgery for pulmonary tuberculosis. The period of time covered in this series was 95 months, Jan. 1, 1945, to and including Nov. 30, 1952. In this interim there were 13,770 deliveries and 236 cases of tuberculosis in term or near-term pregnancy including the 25 patients who were treated by thoracic surgical methods. The incidence of tuberculosis in pregnancy was 1 case for each 59 term or near-term pregnancies, or 1.71 per cent. The incidence of tuberculosis at Bellevue Hospital was 1 case in every 56 pregnancies, 1.83 per cent, while that at New York Lying-In Hospital was 1 case in every 125 pregnancies, 0.82 per cent.

These figures like those of other city hospitals are large, though comprehensible when we consider that our service provides obstetric care for the tuberculosis unit of the West Pavilion of the Metropolitan Hospital, the Chest Clinic of the Welfare Island Dispensary, and receives also a moderate number of tubercular pregnant women from other city institutions through emergency ambulance assignment. Further, it is routine on our obstetrical service to include an antepartum chest x-ray of every pregnant patient. The incidence of patients who had thoracic surgery prior to or concurrent with pregnancy was 1 case in every 551 pregnant women, 0.18 per cent of the total number of deliveries.

Another factor to be considered in the higher incidence of tuberculosis in pregnancy is the race and social status of our clinic cases. In our series of 25 patients there were 13 Puerto Rican, 4 Negro, and 8 white patients all of whom were indigent cases.

Our patients ranged in age from 18 to 39 years and three-fourths of them were 21 to 30 years of age (Table II).

TABLE II. AGE OF MOTHERS

AGE RANGE (YEARS)	TYPE OF CHEST SURGERY						
	LOBECTOMY	PNEUMONECTOMY		THORACOPLASTY		TOTAL	
		DURING	BEFORE	DURING	BEFORE	NO.	PER CENT
18-20	1		6		4	1	4
21-25			4	1	2	10	40
26-30		2				9	36
31-35	1		1	1		3	12
36-40			1		1	2	8
Total	2	2	12	2	7	25	100

Among the 25 patients in our series, 2 women had a lobectomy, 14 women a pneumonectomy, and 9 women submitted to three-stage thoracoplasty. Two of the 14 operations for pneumonectomy were done during pregnancy. It is interesting to note that the remaining 12 women became pregnant 22 times following pneumonectomy. Two of the 9 patients who had three-stage thoracoplasty were operated on during pregnancy while the remaining 7 women were pregnant 13 times following this procedure. Nine of these 25 patients had more than one pregnancy. One patient bore 3 full-term children by cesarean section, had one therapeutic abortion, and is presently 8 months pregnant, all within the past 6 years. Three others each had 2 pregnancies. Another patient was pregnant three times following resection of the left lung. There was, therefore, a total of 37 pregnancies concurrent with or following major thoracic surgery.

Twenty-one of the 25 patients are still living, a 16 per cent mortality. This is a considerably higher figure than assessed from the world literature,

3.1 per cent. However, it may be true that the unreported case is more often the one in which the result was poor. One of the four deaths occurred three months following delivery and may be considered a maternal death though the remaining 3 patients lived 12, 16, and 21 months following their delivery date. Johnson and associates<sup>33</sup> Ornstein and Epstein,<sup>14</sup> Schaefer,<sup>75</sup> and Cohen and co-workers<sup>40</sup> reported 9.3, 14.6, 19.8, and 20.1 per cent mortality in all types of pregnant tubercular patients. With reference to our selected group Gutheil and collaborators<sup>30</sup> and Rubin and Klopstock<sup>79</sup> both reported 8.3 per cent late mortality in postthoracoplasty nonpregnant tubercular patients. If we do not consider the deaths occurring later than one year following delivery our mortality is two cases, or 8 per cent. Both of these deaths occurred in the thoracoplasty group and both patients were primiparas. Of the remaining two patients who died, one was a primipara. Most authorities do not feel that parity is a factor in the prognosis for the tubercular mother.<sup>40, 73, 75</sup> Our figures are small and probably insignificant on this point. Table III illustrates the distribution of these 25 patients according to the variety and time of chest surgery as related to pregnancy and the outcome of the mother and infant.

TABLE III. NEW YORK MEDICAL COLLEGE SERIES, JAN. 1, 1945, TO OCT. 31, 1952

TYPE OF CHEST SURGERY	PREGNANCY OUTCOME						MATERNAL OUTCOME		
	ABORTIONS		PREMATURE BIRTH		TERM BIRTH		DEAD	LIVING ACTIVE DISEASE	LIVING NO APPARENT ACTIVE DISEASE
	SPONTA- NEOUS	THERA- PEUTIC	DEAD	ALIVE	DEAD	ALIVE			
Lobectomy				1		1	1		1
Pneumonec- tomy									
During				1		1			2
Before	2	4	1	2	1	10	1	1	10
Thoracoplasty									
During			1			1	1		1
Before		1				10	1		6
Total	2	5	2	4	1	23	4	1	20

There were 14 primigravidas, 56 per cent; 6 primiparas, 24 per cent; and 5 patients para ii to para vii. See Table IV for this distribution as related to the variety and relationship of time of the surgery to their pregnancies.

TABLE IV. PARITY

PARITY	TYPE OF CHEST SURGERY						
	LOBECTOMY	PNEUMONECTOMY		THORACOPLASTY		TOTAL	
		DURING	BEFORE	DURING	BEFORE	NO.	PER CENT
Para o	1		8	2	3	14	56
Para i		2	2		2	6	24
Para ii to iv			2		2	4	16
Para v to vii	1					1	4
Total	2	2	12	2	7	25	100

The 37 pregnancies were terminated as normal spontaneous deliveries in 17 cases, 45.9 per cent; by forceps delivery 5 times, 14.5 per cent; by 7 elective low-flap cesarean sections, 18.9 per cent; one by cesarean hysterectomy because of a ruptured uterus after a previous cesarean section. Five pregnancies were interrupted, by dilatation and curettage in 4 instances and partial hysterectomy on one occasion, while the remaining 2 pregnancies were terminated as spontaneous abortions. The interrelationships of the varieties of major chest surgery to the time of its performance and method of termination of pregnancy are demonstrated in Table V.

TABLE V. METHODS OF PREGNANCY TERMINATION

METHOD OF TERMINATION	TYPE OF CHEST SURGERY						TOTAL	
	LOBECTOMY	PNEUMONECTOMY		THORACOPLASTY				
		DURING	BEFORE	DURING	BEFORE	NO.	PER CENT	
Normal sponta- neous delivery	2	2	5	2	6	17	45.9	
Forceps delivery			5			5	14.5	
Elective cesarean section			3		4	7	18.9	
Cesarean hysterec- tomy			1			1	0.8	
Therapeutic abortion		1	3		1	5	14.5	
Spontaneous abortion			2			2	5.4	
Total	2	3	19	2	11	37	100	

The average duration of labor was roughly the same with multiparas as with primiparas, about 10 hours. Among the 17 normal spontaneous deliveries, 7 patients were in labor 0.5 to 4 hours; 6 patients 4 plus to 12 hours, and in 4 cases the total labor duration ranged from 19 to 24 hours. All but one of the 5 forceps deliveries were outlet forceps with a range of time in labor of 2 to 13 hours; the single patient delivered by midforceps labored 23 hours.

The average duration of labor in the 17 normal spontaneous deliveries was 8.7 hours while the average duration of labor in the 5 forceps deliveries was 11.6 hours. Six of the 7 low-flap cesarean sections were performed before labor while the seventh patient was in labor but 4 hours while enroute to the hospital. Three of the elective cesarean sections were repeat operations while a fourth was performed because of a fulminating severe pre-eclampsia with a blood pressure of 230/110, 4 plus proteinuria and 4 plus edema refractory to medical therapy during the thirty-second week. The remaining three cesarean sections were performed early in this series prior to our ultimate policy of awaiting a test of labor. As previously mentioned, one patient had a cesarean hysterectomy, after being brought into the hospital as an emergency and with a history of a prior section. All the therapeutic abortions were performed between 1946 and 1950.

Pudendal block was performed on 8 occasions, gas-oxygen-ether was administered to only one patient, 5 patients received no anesthesia or analgesia because of very rapid labors, 13 received supplemental Demerol while all who had low-flap sections were given a spinal anesthetic except one operated upon recently with local infiltration.

The maternal obstetric complications in addition to the concurrent or previous chest surgery included one case of ruptured uterus, one case of severe pre-eclampsia and two spontaneous abortions at 2 and 2.5 months. One patient also was treated during pregnancy for secondary syphilis. Dyspnea during pregnancy or labor was not a factor in any of our cases. This agrees with the findings of Seeley and associates<sup>37</sup> but not with those of Jameson,<sup>10</sup> Mueller,<sup>59</sup> Boquist and co-workers,<sup>62</sup> McIntyre,<sup>68</sup> and Koske,<sup>66</sup> among others.

The time elapsed between the first major chest surgery and the first subsequent pregnancy was 1 to 3 months in 4 cases; 7 to 12 months in 2 cases; 1 to 3 years in 14 cases, and 3 to 4 years in 5 cases. Table VI shows the distribution of this time interval.

TABLE VI. TIME INTERVAL BETWEEN FIRST MAJOR CHEST SURGERY AND FIRST SUBSEQUENT DELIVERY

TYPE OF CHEST SURGERY	TIME INTERVAL RANGE				TOTAL	
	1-3 MONTHS	7-12 MONTHS	1-3 YEARS	3-4 YEARS	NO.	PER CENT
Lobectomy			1	1	2	8
Pneumonec- tomy						
During	2				2	
After			8	3	11	52
Thoracoplasty						
During	2				2	
After		2	5	1	8	40
Total	4	2	14	5	25	100

Among the 37 progeny of these 25 mothers 7 resulted in therapeutic or spontaneous abortions and each fetus weighed less than 500 grams. There were 4 infants born with premature weights, 11.8 per cent, and 3 of these babies are still alive, 75 per cent. This is hardly more than the usual incidence of premature births of all types. The one premature death of the 2,100 gram baby occurred on the third postpartum day. There were 26 near-term or at-term infants all of whom weighed more than 2,500 grams, 70.3 per cent, and 24 of these 26 infants were presently alive and well, 92.3 per cent. These two deaths included the 2,900 gram still born infant of the patient with the ruptured uterus, while the second infant died at the age of 19 months of tuberculous meningitis. Parenthetically, it is noted that the mother of this infant is alive and exhibits no signs of active disease, while the father to whom the care of the baby was entrusted also died of tuberculous meningitis. The smallest baby weighed 1,480 grams and the heaviest 3,930 grams. The average birth weight was just over 3,000 grams which is about the average birth weight among our predominantly Puerto Rican and Negro patients. Table VII illustrates the weight of the infants to the time and the variety of chest surgery on the mother.

TABLE VII. WEIGHT OF INFANTS

WEIGHT IN GRAMS	TYPE OF CHEST SURGERY						
	LOBECTOMY	PNEUMONECTOMY		THORACOPLASTY		TOTAL	
		DURING	BEFORE	DURING	BEFORE	NO.	PER CENT
Below 500		1	5		1	7	18.9
1,000-1,500			1			1	
1,501-2,000							11.8
2,001-2,500		1	1	1		3	
2,501-3,000	1		6		2	9	
3,001-3,500	1	1	4	1	6	13	70.3
3,501-4,000			2		2	4	
Total	2	3	19	2	11	37	100

Two of the 4 deaths of mothers were caused by the development of bronchiogenic fistula with massive pulmonary collapse 3 and 12 months following delivery and 21 and 24 months, respectively, following their primary major thoracic surgery. One mother died of widespread pulmonary tuberculosis 57 months after a lobectomy and 21 months post partum. The remaining mother died of far-advanced generalized tuberculosis with amyloid disease of the liver and kidneys 29 months following her three-stage thoracoplasty and 16 months following her delivery. Table VIII illustrates a summarized analysis of these deaths.



TABLE VIII. ANALYSIS OF DEATHS OF MOTHERS

STUDY CASE NO.	TYPE OF CHEST SURGERY	DATE OF CHEST SURGERY	DELIVERY DATE	DATE AND CAUSE OF DEATH OF MOTHER
3	Lobectomy	Sept., 1946	Sept. 14, 1949	June 13, 1951. Far-advanced pulmonary tuberculosis
15	3 stage right thoracoplasty	Dec., 1946	Jan. 1, 1947	Jan. 2, 1948. Bronchiogenic fistula, pulmonary collapse
17	3 stage left thoracoplasty	May, 1945	June 14, 1946	Oct. 4, 1947. Far-advanced tuberculosis; amyloid disease of liver and kidneys
27	Resection of right lung	Feb., 1948	Feb. 2, 1952	May 11, 1952. Bronchiogenic fistula, pulmonary collapse

Among the surviving patients there is but a single one exhibiting evidence of tuberculous activity while in the remaining 20 cases there is no demonstrable evidence of reactivity of tuberculosis.

### Summary

Over a period of 95 months, Jan. 1, 1945, to and including Nov. 30, 1952, there were 25 women who became pregnant 37 times during or subsequent to major thoracic surgery employed to control extensive unilateral pulmonary tuberculosis. The three major chest surgical procedures considered in correlation with pregnancy included lobectomy in 2 cases, pneumonectomy in 14 cases, and three-stage thoracoplasty in 9 women. This series is compared to 119 cases of thoracoplasty and 8 cases of lobectomy or pneumonectomy during or prior to pregnancy derived from the literature.

There were 4 maternal deaths in our series, 16 per cent. Among the 37 progeny there were 10 infants lost through abortion, spontaneous on 2 occasions, therapeutic in 5 instances, one stillbirth following rupture of the uterus, and 2 infant deaths; one infant died of prematurity at 3 days and one 19-month-old infant died of tuberculous meningitis. Among the 21 surviving mothers only one exhibits tuberculous activity after pregnancy following or concurrent with major chest surgery.

These figures compare favorably with those collected from the literature.

### Conclusion

In conclusion we reiterate that our original goal was to determine any possible interrelationship between pregnancy subsequent to or concurrent with major thoracic operations on tubercular patients. From the obstetrical viewpoint solely there are four principal findings:

1. Pulmonary tuberculosis can be treated prior to or during pregnancy with major thoracic surgery without jeopardizing the pregnancy.
2. Major thoracic surgery for pulmonary tuberculosis prior to or during a pregnancy is not an indication for therapeutic abortion.

3. The course of labor, the management at delivery, and the prognosis for the infant do not differ from those in the tubercular patient who has not undergone such surgery.

4. The evidence seems to indicate that lung resection is a more favorable procedure than thoracoplasty with regard to the maternal outcome in a subsequent pregnancy.

We wish to extend our gratitude and appreciation to Dr. Salvatore Carrabba, former resident at the Metropolitan Hospital, Department of Obstetrics and Gynecology, for his assistance in partial collation of clinical records, and to Miss Eva Ader, Medical Social Worker, Welfare Island Dispensary, Metropolitan Division, for her splendid efforts in making possible the complete accuracy of the follow-up of patients and their infants in this study.

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### Discussion

DR. ALFRED C. BECK, Brooklyn, N. Y.—From the changes that take place normally in pregnancy which alter the thoracic cage, and result in an increase in vital capacity, we would think that interference with these changes would jeopardize the chance of having a living child. I was, therefore, surprised to see the results in this respect. Were any tests made of vital capacity, tidal air, and so forth, in the course of the pregnancy in these cases?

Do you think, as a result of your studies, that pregnancy should be permitted in such parents? We all dislike abortions but most of us do not hesitate to advise contraception. Experience such as you have reported might lead us to recommend the avoidance of pregnancy in some of these cases. Is that your opinion?

DR. I. C. RUBIN, New York, N. Y.—This report can be reckoned as an item of progress because certainly the relationship between thoracic surgery for tuberculosis and the eventuality of pregnancy is not commonly known in obstetric practice. I should have been at a loss in the management of such a patient. Although twenty-five cases is not a large series, this combination is probably going to occur more often in the future because tuberculosis of the chest will be attacked more and more safely and successfully.

DR. SAMUEL A. COSGROVE, New York, N. Y.—Dr. Rubin has said that this was a small series. That is, of course, true, but thoracic surgery itself is one of the infants of the specialties, and up to this time has had only limited application to tuberculosis itself, much less to tuberculosis in the pregnant woman. Dr. Folsome's series is the largest yet reported from any single clinic.

DR. ROBERT S. MILLEN, Westbury, N. Y.—Tuberculosis chest survey films are a prerequisite for admission to the obstetrical section of The North Country Community Hospital in Glen Cove. During the past six years more than six thousand x-ray pictures have been taken and, although a small number of lesions have been found and shown by additional large films to be apical fibrosis or a minimal healed tuberculous lesion, there have actually been found only two lesions of active tuberculosis. I mention these figures to point out that active tuberculosis is not as common in all localities.

DR. F. C. FREED.—To answer Dr. Millen's point, the population he has in Glen Cove is quite different than at Harlem Hospital.

DR. HENRY S. ACKEN, JR., Brooklyn, N. Y.—It has been my good fortune to have some experience with this problem of tuberculosis in pregnancy. Some of those patients have had thoracoplasty operations and they did well.

I would like very much to substantiate the statement made by Dr. Folsome in regard to these patients. They go through their pregnancies and withstand normal labor extremely well.

One thing that should be stressed is the fact that these patients should not be subjected to undue labor, but should have cesarean section if there is evidence of uterine inertia or any marked pelvic disproportion. Since my small series were all private patients and were cared for by phthisiologists, we have been able to follow them very carefully throughout a long period. There have been no deaths whatever over that extended period of time.

The incidence of prematurity has been low, as Dr. Folsome has suggested, and the babies have done extremely well.

One of the things that impressed me very much in going over my own series was the fact that the babies were unusually large. The vast majority of them weighed 8 pounds or over.

DR. CHARLES M. McLANE, New York, N. Y.—I can add nothing to Dr. Folsome's paper because I have seen no patients delivered after major thoracic surgery for tuberculosis. I can corroborate Dr. Posner's figures on the increase in the incidence of undiagnosed pulmonary tuberculosis picked up by the routine x-raying of all obstetrical patients in the obstetrical clinic of the New York Hospital. In the past 4 or 5 years our incidence has increased from 0.5 to 1.5 per cent. It is possible that if routine chest x-rays were taken on all obstetrical patients, more of them would not later have to have thoracic surgery.

DR. ARTHUR V. GREELEY, New York, N. Y.—I have a very small series of cases, in fact consisting of one patient with a pneumonectomy. This patient presented a problem because she had very marked tachycardia and very low vital capacity and was unable to lie flat in bed. She presented more of a problem from a cardiac standpoint than from the pulmonary. She had a positive sputum during the latter part of her pregnancy. When she came to delivery, the labor was very easy and uneventful. She was a primipara. She was delivered in a semi-upright position with pudendal block and low forceps. It is about three years now, I think, since delivery and she has done well. The baby has done well. I wondered if that problem has presented itself in any of your cases, the question of tachycardia and low vital capacity.

DR. BERNARD J. PISANI, New York, N. Y.—I thought you would be interested to know that within the structural framework of the Veterans Administration, with its tremendous numbers of tuberculous veterans, about one-twelfth of the veterans' population with tuberculosis are women. They have had, within the last 24 months, 12 patients throughout the country who have had pregnancies after major surgery, with results that, as far as I know, concur with Dr. Folsome's results.

Within the past year here in this city there have been two patients with segmental resections who have been delivered with good results. One was done by Dr. Chambers and one by Dr. Miscal.



DR. FOLSOME (Closing).—We did review the vital capacities of these patients. We became aware then that this aspect of these cases was of more value in a larger series of cases than in this special subseries. In a subsequent paper concerned with 236 cases of tuberculosis associated with pregnancy we plan to evaluate the more detailed vital capacities with the phthisiologists. Because of the variables in these problems we confined the present paper exclusively to the obstetrical aspects in this special group of women pregnant following major surgery.

In reply to those who inquired about tachycardia and dyspnea itself, we found no significant change in any of these 25 patients though we did make a meticulous search for these particular symptoms. In a review of these cases we could find no unusually different pulse or respiratory rates from those seen in normal labor.

As Dr. Freed pointed out, we did note an increased incidence of tuberculosis in the pregnant clinic cases as opposed to the private cases, 1.71 per cent as opposed to 0.8 per cent. At Bellevue Hospital, a city institution much like ours, the rate was 1 tuberculous pregnant patient to each 56 nontuberculous maternal cases. At Metropolitan the incidence was 1 to 59 cases while at New York Lying-In Hospital the rate was 1 case in 125 maternal cases, or half as frequent.

In regard to our choice of method for termination of pregnancy we find, as Dr. Acken so well points out, that cesarean section is definitely not the answer. During the first four years of this study the section rate was higher primarily because the obstetricians permitted the thoracic surgeons to decide that cesarean section was the approved method of termination of pregnancy. Since 1950, however, and up to the present time, our obstetricians have individualized every case primarily upon their obstetrical judgment. It is interesting to report that they have, since 1950, obtained a lowered section rate. In fact, excluding one patient sectioned primarily because of an abruptio with a fulminating toxemia, the only sections done in this type of case were in those patients who had been delivered by cesarean section earlier. Thus the main indication in this small group was repeat section.

Earlier, the added socioeconomic factors of the pregnant tubercular patient evidently did enter into the medical decision to interrupt such pregnancies. These have not been factors in the past four years. Between 1945 and 1950 there were 5 therapeutic abortions in this small series of patients; however, since 1950, during which period we have had more pregnancies in patients following major thoracic surgery, there were no therapeutic abortions.

The obstetrical burdens appear, in our experience, to be more easily tolerated by patients whose tuberculous process was treated by lung resection. The burden of pregnancy seemed to be less well tolerated by patients previously treated by three-stage thoracoplasty. We note that the lung resection group, however, were generally younger, so that age and a lessened prior surgical trauma may be partly responsible for our better results in the pneumonectomy group. The thoracoplasty group in our series fell principally in the age range of 26 to 31 years, while the lung resection group were on the whole several years younger. Likewise, the prior tuberculous process had existed longer in the thoracoplasty group, hence the degree of tissue destruction or surgical trauma may be an additional factor.

Again, in summary, we subscribe to the principle that the management of each pregnancy is a highly individualized process and that tuberculosis treated by major thoracic surgery and controlled properly by this means does not alter our subsequent obstetrical management.

## CONCURRENT ASSOCIATION OF TRICHOMONAS VAGINALIS, THE FILIFORM BACILLUS OF DÖDERLEIN AND SYRINGOSPORA IN PREGNANCY

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A STUDY<sup>1</sup> evaluating the presence of the long strain of the lactobacillus of Döderlein in the vagina of pregnant women yielded considerable data concerning the incidence of association of this organism with *Trichomonas vaginalis* and the pseudomycelia-producing, yeast-like organisms of the genus *Syringospora* (Candida). Surveys on the incidences of the three organisms have been published in excellent reviews of the literature.<sup>1-7</sup> However, I know of no report on the concurrent infections although a few workers have presented some data on this problem relative to their primary studies.<sup>8-14</sup>

The purpose of this paper is to present the incidences in late pregnancy of *Trichomonas vaginalis*, the long strain of the bacillus of Döderlein, and the yeast-like infections and to report the incidences of association of the three organisms.

### Materials and Methods

Saline suspensions of the vaginal discharges of regularly attending pre-natal patients were prepared. Immediately the wet-mounts were examined microscopically for the presence of trichomonads, the filaments of Döderlein's bacillus, and the pseudomycelia of *Syringospora*. The wet readings of an occasional to a few organisms were graded plus one (+) and those estimated as moderate to many numbers of organisms per low-power field were designated as plus four (++++).

All patients examined were in their third trimester of pregnancy. During this period of gestation all intravaginal manipulations are interdicted and the vaginal flora is less likely to be disturbed.

### Results

The vaginal discharges of 500 Negro and 200 white pregnant patients were examined. In the white group, 33 patients, or 16.5 per cent, were infected by *Trichomonas vaginalis*; 24 patients, or 12.0 per cent, harbored a species of *Syringospora*; and 1 patient showed the long strain of the bacillus of Döderlein. Higher incidences were found in the Negro group. Of 500 Negro pregnant women examined, 218, or 43.6 per cent, were found to harbor *Trichomonas vaginalis*; 115 patients, or 23.0 per cent, were infected with *Syringospora*; and 76 pregnant women, or 15.2 per cent, revealed the filaments of Döderlein's lactobacillus.

Table I presents the data according to estimated numbers of organisms observed microscopically. While 149, or 74.5 per cent, of the white women attending the Jefferson Prenatal Clinic were free of the three organisms, only 43.6 per cent of the Negro patients showed absence of these same organisms.

TABLE I. THE INCIDENCE OF *TRICHOMONAS VAGINALIS*, THE FILIFORM BACILLUS OF DÖDERLEIN AND *SYRINGOSPORA* IN LATE PREGNANCY

TOTAL PATIENTS EXAMINED	TRICHOMONAS VAGINALIS		BACILLUS OF DÖDERLEIN		SYRINGOSPORA	
	+	++++	+	++++	+	++++
White 200	19	14	1	0	13	11
Total per cent positive	16.5		0.5		12.0	
Negro 500	123	95	36	40	82	33
Total per cent positive	43.6		15.2		23.0	

Table II presents the incidences of double infections found in this survey. As is to be expected from the above incidences of single infections, the Negro group had the higher percentages of multiple infections. None of the white patients harbored the three organisms concurrently, but 22 Negro women, or 4.4 per cent, showed the presence of all three.

TABLE II. THE INCIDENCE OF CONCURRENT *TRICHOMONAS VAGINALIS*, THE FILIFORM BACILLUS OF DÖDERLEIN AND *SYRINGOSPORA* INFECTIONS IN LATE PREGNANCY

TOTAL PATIENTS EXAMINED	TRICHOMONAS VAGINALIS AND BACILLI OF DÖDERLEIN	TRICHOMONAS VAGINALIS AND SYRINGOSPORA	BACILLI OF DÖDERLEIN AND SYRINGOSPORA
White 200	1	6	0
Percentage positive	0.5	3.0	0
Negro 500	62	61	26
Percentage positive	12.4	12.2	5.2

Patients in whom the vaginal flora showed large numbers of one of the three organisms presented the most interesting data on the concurrent association of the infections. In the white group there were three cases showing maximum (++++ ) numbers of *Trichomonas vaginalis* with the yeast infection and likewise three cases with the numerous yeast-like organisms accompanied by a trichomonad infection. In two of these patients maximum numbers of trichomonads and the pseudomycelia occurred together. In the Negro group a plus four (++++ ) *Syngospora* infection showed a 60.6 per cent infection by trichomonads, 8 patients presenting great numbers of both organisms. In this same group the long strain of the bacillus of Döderlein occurred in 24.2 per cent with great numbers of both organisms present in 7 patients. A plus four (++++ ) reading of *Trichomonas vaginalis* was associated with a species of *Syngospora* in 28 cases and with the bacillus of Döderlein (long strain) in 14, a percentage of 29.5 and 14.7, respectively. In the former group 8 patients harbored many numbers of both organisms while of the latter group there were 14, or 100 per cent. The association of *Trichomonas vaginalis* with the long strain of Döderlein's bacillus is emphasized further by the following percentage. Thirty-seven patients, or 92.5 per cent, harbored trichomonads in a plus four (++++ ) environ-

ment of the filamentous bacillus of Döderlein. Eighteen patients, or 54.5 per cent, showed a species of *Syringospora* in the same milieu. Fourteen patients of the former group showed maximum numbers of the organisms occurring together, while there were 7 patients of the latter group.

### Comment

It is quite evident that the three organisms may exist in the vagina of the pregnant woman entirely independent of one another and the figures also indicate a coincidental incidence rather than a habitual association. Although the patients in this survey were in their last trimester of pregnancy, during which period there is the trend to increased normality of the vaginal flora, the percentage incidence of *Trichomonas vaginalis* compares favorably with the higher incidences as reported in the literature.<sup>15-18</sup>

But the important observation of this study and one that has not been fully realized and emphasized in the literature is the propensity of *Trichomonas vaginalis* to survive in association with the bacillus of Döderlein and species of *Syringospora* in an acid environment of low pH range. In the patients with environmental conditions optimum for the growth of *Syringospora*, 60.6 per cent revealed *Trichomonas vaginalis*. However, when the environment was conducive to the propagation of the protozoan, 29.5 per cent showed the presence of a species of *Syringospora*. Surprisingly, *Trichomonas vaginalis* persisted in 92.5 per cent of patients harboring maximum numbers of the filamentous strain of the bacillus of Döderlein. In this latter group the pH readings of the vagina ranged between 3.6 to 4.7.<sup>1</sup>

Present-day therapy of *Trichomonas* vaginitis includes acid medicaments with the view of restoring the normal pH level of the vagina, inducing the growth of the lactobacillus of Döderlein, and re-establishing a normal bacterial flora. It is therefore of considerable interest to know that *Trichomonas vaginalis* will survive in the vagina with a pH range of 3.6 to 4.7 and in the presence of the bacillus of Döderlein.

### Summary

1. Saline mounts of the vaginal discharges of 500 Negro and 200 white women in their last trimester of pregnancy were examined microscopically for *Trichomonas vaginalis*, the filamentous strain of the bacillus of Döderlein, and the pseudomycelia of *Syringospora*.

2. In the white group the percentage incidences of the above organisms were 16.5, 12.0, and 0.5, respectively. There was one case of double infection with *Trichomonas vaginalis* and the bacillus of Döderlein and 6 cases showed both trichomonads and *Syringospora*.

3. In the Negro group *Trichomonas vaginalis* occurred in 43.6 per cent of the patients, *Syringospora* in 23.0 per cent, and the filaments of the bacillus of Döderlein in 15.2 per cent. The concurrent association of trichomonads with Döderlein's bacillus, trichomonads with *Syringospora* and the bacillus of Döderlein with *Syringospora* was observed in 12.4 per cent, 12.2 per cent, and



5.2 per cent, respectively, of the Negro patients. Concurrent infection with the three organisms occurred in 22 patients, or 4.4 per cent.

4. *Trichomonas vaginalis* survives in an environment optimum for the growth of *Syngospora* or the bacillus of Döderlein (long strain). In the Negro group with a plus four (++++) *Syngospora* infection, *Trichomonas vaginalis* was present in 60.6 per cent of the patients. In a plus four (++++) environment of the filamentous bacillus of Döderlein, 92.5 per cent of the Negro patients harbored *Trichomonas vaginalis*.

Appreciation is expressed to Dr. Lewis C. Scheffey and Dr. Thaddeus L. Montgomery for the facilities of their department and to Dr. David H. Wenrich, Department of Zoology, University of Pennsylvania, for his helpful comments.

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## THE DELIVERY OF A QUADRIPLÉGIC PATIENT CONFINED TO A RESPIRATOR

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THE problem of antepartum care and delivery of a woman who has been a victim of poliomyelitis with resulting quadriplegia is fortunately rarely encountered but is not necessarily insurmountable. In the present case, although death finally resulted from renal complications of the quadriplegic state, delivery from below had been accomplished.

In 1906, Cushny<sup>1</sup> established the fact that the automatic rhythmic uterine contractions are myogenic, rather than neurogenic, and that completion of the first stage of labor is possible after severance of all nerves to the uterus. It has been demonstrated that the uterus will contract after division not only of the spinal cord but also of the sympathetic nerve supply to the uterus. Uterine contractions have been noted in poliomyelitis victims and in patients paralyzed as a consequence of tumor of the cord, spondylitis and vertebral fracture.<sup>2</sup>

After the cervix is fully dilated and the head has descended to a low station, complete paralysis of all the voluntary muscles with the absence of the so-called secondary forces of labor definitely hinders the progress of the second stage of labor. Paralysis of the bladder and distention of that organ and of an atonic bowel may interfere with the normal third stage of contractions, thus increasing the possibility of hemorrhage at this time. Paralysis and overdistention of the bladder and bowel during pregnancy, with constantly reforming fecal impactions, necessitate frequent cathartics and enemas which may accentuate the Braxton Hicks contractions, and premature labor may be induced.<sup>3</sup> Renal infections are also prone to occur due to the overdistention and incomplete emptying of the bladder. These may be cystitis or ascending infections leading to pyelonephritis. Marked distention of the large intestine caused by fecal impactions may produce pressure on the paralyzed diaphragm and may increase an already serious hypoxia.<sup>4</sup>

In their study, Kleinberg and Horwitz<sup>2</sup> found roentgenographic evidence of some degree of pelvic asymmetry in 79.21 per cent of 101 paralytic women. While the incidence of "deformed pelvis" was high, the degree of contraction or flattening noted was generally slight, and only exceptionally was it marked. The following factors were considered in association with pelvic deformity: (1) the effect of associated lumbosacral scoliosis, (2) the role of weight-bearing, especially as influenced by the use of external appliances and reconstructive procedures, (3) the shortening of a lower limb, (4) muscle imbalance due especially to paralysis of the pelvifemoral and pelvispinal muscles, (5) paralysis

of muscles below the hip. They found that in bedridden patients and, similarly, in patients who walked with crutches and bore little or no weight on their legs, the pelvis remained large and fairly symmetrical.

Helms,<sup>5</sup> Morrow and Luria,<sup>6</sup> McGoogan,<sup>7</sup> Peelen,<sup>8</sup> and Lewin<sup>9</sup> all seem to be of the opinion that emptying of the uterus should be reserved for cases in which the enlargement of the uterus is sufficient to hamper respiration by encroachment on the paralyzed diaphragm, and in which respiration and lung aeration will be facilitated by delivery. Lewin also advocates this procedure in cases in which there is severe cystitis or other complications. The incidence and types of complications of pregnancy have been noted to be practically the same in the paralytic and nonparalytic woman.<sup>2</sup>

L. A. was a 29-year-old white housewife. She had quadriplegia which was a sequela of an attack of poliomyelitis in 1949. At that time, she spent six months in a respirator at another hospital. This was followed by rehabilitation therapy until August, 1950, when she left that hospital against advice. During the period of treatment she had been home for brief visits. Her last normal menstrual period had been in March, 1950. Previously she had had two normal pregnancies which had terminated in normal deliveries. The larger baby had weighed 6 pounds, 8½ ounces at birth. The patient had no untoward symptoms during the third pregnancy until three weeks prior to her admission to the Meadowbrook Hospital on Sept. 21, 1950. At that time she began to have dyspnea which became progressively more severe.

The patient was well developed, but poorly nourished and emaciated. She had generalized atrophy and paresis of the musculature of the trunk and all extremities. Mild respiratory distress was present. The temperature was 98.6° F., the pulse rate 80, the respiratory rate 23 per minute, and the blood pressure 120/80. The physical examination was not otherwise remarkable. The uterus contained a vertex presentation in the left occiput transverse position which was unengaged. The fundus extended 18 cm. above the symphysis pubis. The fetal heartbeat was heard in the left lower quadrant of the abdomen at a rate of 136 per minute. The red blood cell count was 4.10 per c.mm. and the hemoglobin level was 11.6 Gm. per 100 c.c., or 80 per cent. The urinalysis revealed 5 to 10 red blood cells and 5 to 7 white cells per high-power field.

During the first few hospital days, the patient did well and required a respirator only during the hours of sleep. On the eleventh and thirteenth hospital days she passed grossly bloody urine and had slight tenderness in the flank. A flat film of the abdomen was made on the nineteenth hospital day which showed a single 6-month fetus and calcifications to be present in the right lower and left upper abdominal quadrants. An intravenous pyelogram was made on the twenty-first hospital day, but was unsatisfactory because of the difficulty in preparing a quadriplegic patient. However, the film suggested that the calcification in the left upper quadrant was a renal calculus. During the ensuing days, the patient had occasional bouts of hematuria, and became increasingly dependent on the respirator until she was able to remain out of it for only 20 minutes at a time. Attempts were made to accustom the woman to the use of a positive pressure hood, anticipating delivery, but these were met with minimal success because of the patient's extreme apprehension in the hood.

On the evening of the sixty-first hospital day, the patient began to complain of intermittent epigastric and left upper quadrant pain which was not accompanied by observable uterine contractions. The pain continued the next day and abdominal distention was progressive. On the sixty-fourth hospital day the abdomen was tympanic, hyperactive bowel sounds were heard, and dilated loops of small intestine were seen through the thin abdominal wall. Pelvic examination revealed no masses, an unengaged vertex presentation displaced to the left, and a long closed cervix. A flat film of the abdomen revealed scattered distention of both the large and small bowels which was suggestive of a mild ileus,

but there was no evidence of intestinal obstruction. A Cantor tube was inserted and Wangenstein suction was started. Surgical intervention was believed to be contraindicated, and Wangenstein drainage was continued. Intravenous therapy was employed to retain electrolytic balance. On the seventieth hospital day the patient passed three formed stools, the last being hard and about the size of a small orange. Following this, the abdominal distention subsided. After this episode, she followed a more or less uncomplicated course in the respirator with occasional attacks of mild distention of the bowel and occasional faintness. One remarkable episode of severe faintness, cyanosis, and apprehension occurred while she was in the positive pressure hood of the respirator. Subsequently all attempts to use the hood were abandoned.

On the evening of the one hundred seventh hospital day the patient went into labor spontaneously. After an uncomplicated first stage of eight hours and thirty minutes and a second stage of one hour and forty minutes under light Nembutal, Demerol, and scopolamine, she was delivered by low forceps extraction from a right occiput anterior position because of an absence of the secondary forces of labor. A 1 per cent procaine pudendal block anesthesia was administered. Delivery was accomplished by alternately pulling the woman in and out of the respirator on a dolly, since she was able to remain out of the respirator only about seven minutes at a time. The result was the birth of a living male infant who weighed 5 pounds, 13 ounces, who subsequently developed bilateral cephalhematomas. An intravenous preparation of Ergotrate was administered with the delivery of the anterior shoulder; the placenta was expressed after a ten-minute third stage. There was a third-degree laceration extending through the rectal sphincter which was repaired.

Following delivery, the patient was given procaine penicillin, 300,000 units twice daily, for 14 days as a prophylactic measure. She made a dramatic recovery from the previous antepartum respiratory distress, so that she was able to remain out of the respirator almost all of the time by the sixth postpartum day (one hundred thirteenth hospital day). The laceration healed well, and the uterus involuted without any evidence of endometritis or parametritis.

The woman was admitted to the hospital several times during the following year or more, and was shown to have kidney stones by cystoscopic and retrograde pyelographic examination. She finally died in renal failure.

### Summary

The literature is reviewed, and a case of the management and delivery from below of a quadriplegic patient, confined to a respirator, is reported.

The patient, who had been partially rehabilitated and taught to breathe by using her diaphragmatic musculature, was seen after the fifth month of gestation. She had begun to have progressive respiratory difficulty, necessitating increasing periods of confinement in a respirator. The complications were those of a paralyzed respirator patient and not those of pregnancy. Conservative management of renal stones with concomitant pyelonephritis was carried out. Nonsurgical management of a temporary intestinal obstruction caused by a high fecal impaction was necessary. Labor progressed normally, but delivery was complicated by the absence of the secondary forces of labor, necessitating operative intervention in the second stage. Recovery during the postpartum period, both obstetrically and as to respiratory status, was rapid and remarkable.

This case was observed at the Meadowbrook Hospital, East Hempstead, Long Island, while the author was a resident there, and it is presented with the kind permission of Dr. E. Freeman Miller, Chairman of the Division of Obstetrics.



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## HEMOLYTIC ANEMIA IN PREGNANCY

### Report of Two Cases

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**H**EMOLYTIC disease is a rare but serious complication of pregnancy. Recent literature on the subject is almost nonexistent. The only article available dealing specifically with hemolytic anemia in pregnancy is that by Johnson and McAllister,<sup>1</sup> who cited a case of congenital hemolytic anemia in crisis in the third trimester. The patient was treated conservatively with multiple transfusions, and at term delivered a living normal infant. Other articles not specifically dealing with hemolytic disease in pregnancy mention its occurrence and therapy in connection with the general topic of splenectomy. The most extensive and complete of these articles is the paper by McElin, Mussey, and Watkins<sup>2</sup> of the Mayo Clinic. They found in the literature only 50 reported cases of splenectomy during pregnancy. Of these only two patients were operated on because of congenital hemolytic anemia. They added to the literature five more cases of splenectomy during pregnancy of which three were congenital hemolytic anemia. Barnes and Doan<sup>3</sup> reported three cases of splenectomy during pregnancy, one of which was indicated by the presence of hemolytic anemia. Another case, not sufficiently documented to report, was also mentioned. Shellhouse and Morris<sup>4</sup> reported a case of a family having chronic hemolytic anemia. The mother had been carried through two pregnancies in which hemolytic crises had been treated by multiple transfusions. Following the second pregnancy a splenectomy was performed. She subsequently became pregnant again and delivered uneventfully. Shortly thereafter all three children, at different times, became seriously ill with severe hemolytic crises and splenectomies had to be performed on all three.

The clinical characteristics and laboratory findings in congenital hemolytic anemia are well known. The two most important factors in establishing the diagnosis are the occurrence of increased fragility of the red cells, and the presence of spherocytosis on a stained blood smear. Except for its being more severe, there are no essential changes in the disease during pregnancy. Although pregnancy does not cause hemolytic anemia, it may be a precipitating factor.

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We are reporting the following cases in considerable detail because of the severity of the disease, its complications, and its nearly fatal outcome.

### Case Reports

CASE 1.—This 22-year-old white woman, gravida i, para 0, was first seen in the Prenatal Clinic of the Fort Monmouth Army Hospital on Aug. 14, 1951. Menses had begun at the age of 15 years. Until the onset of this pregnancy her menstrual periods occurred regularly on a 28 day cycle and lasted from 5 to 6 days. There was no history of recent drug ingestion. The dietary history and system review were within normal limits. The weight gain in the first six months of pregnancy was only 6 pounds. The expected date of confinement was Oct. 24, 1951.

Review of the family history revealed the following facts: Her father, aged 51, was said to have had hemolytic jaundice 10 years earlier. A splenectomy had been advised, but deferred because of gradual improvement. No recurrent hemolytic crises occurred.

Her mother, aged 48, had been told in her youth that she was very anemic. Splenectomy had been advised at various times throughout her life because her spleen was enlarged. However, no hemolytic crises were noted in her 10 pregnancies. Two of the patient's brothers were reported to have had anemia, one of whom had recently had a splenectomy.

The patient's last normal menstrual period was Jan. 18, 1951. She was first seen by a physician in Texas and the diagnosis of pregnancy made on June 6, 1951. The physical examination on that date was recorded as normal. However, because of slight jaundice of the scleras some diagnostic blood tests were ordered and all were within normal limits. Unfortunately the hemogram reports done at the time of that visit are not available. At the time of the next visit, on July 6, 1951, the jaundice had disappeared and no further investigation was carried out.

She then traveled by automobile from Texas to New Jersey without apparent ill effect, and was seen as a routine case in the Prenatal Clinic of the Fort Monmouth Army Hospital. She stated that the first 28 weeks of pregnancy seemed completely normal. There were no definite symptoms of anemia, no jaundice, vertigo, melena, hematuria, dyspnea, or fainting.

In the two weeks prior to her visit to the Prenatal Clinic she had noted increased fatigue on very mild exertion together with dyspnea and swelling of the ankles. Her extreme pallor was immediately striking and alarming. An emergency complete blood count was reported as showing a red blood count of 1,170,000 with 6.5 Gm. of hemoglobin. Because of this severe anemia the patient was immediately admitted to the Obstetrical Ward.

The positive physical findings on admission were: blood pressure, 120/60; temperature, 98.6° F.; pulse, 120; respirations, 32. The scleras were noted to be slightly icteric and the thyroid palpable. Respirations were short and rapid, but the lung fields were clear and resonant. The heart was enlarged to 1 to 2 cm. to the left of the midclavicular line. There was a Grade II systolic precordial murmur which was not transmitted. The rate was rapid but regular. Examination of the abdomen revealed slight epigastric tenderness. The liver was 3 to 4 fingerbreadths below the right costal margin. The spleen descended to well below the iliac crest, its lower edge could not be felt and it was hard and nontender. The fundus extended 2 cm. above the umbilicus. The fetus was presenting vertically and the heart tones were 140 in the right lower quadrant. There was bilateral 3 plus ankle and pretibial edema with bronze discoloration of the feet and ankles on the dorsal surface. The skin, in general, was extremely pale and lemon yellow in color.

Laboratory work done on admission revealed: red blood count, 1,190,000; hemoglobin, 6.5 Gm.; hematocrit, 12; white blood count, 8,850 with a normal differential. Polychromatophilia, normoblasts, microblasts, and megaloblasts, together with basophilic stippling, were noted on the stained blood smear. The urine test was essentially normal. The chest x-ray revealed increased bronchovascular markings. The serologic test was negative.

On August 15, the day following admission, she was seen by the Medical Service and a marrow puncture unsuccessfully attempted. She was fairly comfortable throughout the day. Pulse and respiratory rate remained high but regular. No further signs of cardiac decompensation secondary to the anemia were noted. The Medical Service agreed with our initial impression of hemolytic disease in crisis, but transfusion was deferred until the diagnosis could be confirmed. The patient had an evening temperature of 100° F.; pulse, 140; respirations, 26, probably secondary to hemolytic process. The prognosis, in general, was poor. It was felt that splenectomy could not be done until further transfusions were given. Interruption of the pregnancy of 28 weeks' duration was likewise contraindicated. The blood picture on that day was essentially unchanged: red blood count, 1,540,000; hematocrit, 12; hemoglobin, 6.5 Gm.; blood type, A, Rh positive. Howell-Jolly bodies were noted in the peripheral smear. A malarial smear was reported as negative.

A successful marrow puncture on August 16 revealed:

megaloblasts	46%
macroblasts	11%
erythroblasts	2%
normoblasts	4%
microblasts	1%
eosinomyeloblasts	2%
myeloblasts	10%
juvenile forms	6%
bands	6%
segmented polymorphonuclear cells	8%
eosinophils	2%
blasts	1%
lymphocytes	1%

These findings were considered as consistent with hemolytic anemia. This, together with a red cell test that showed increased fragility, confirmed the diagnosis. The fragility test showed fragility as beginning in the patient at 0.72 and ending at 0.39; in the control beginning at 0.51, ending at 0.33.

The Coombs test was negative; nonprotein nitrogen, 27.2; glucose, 83.6; uric acid, 5.3; total protein, 4.96; albumin, 3.42; globulin, 52; albumin/globulin ratio, 2.2/1; chlorides, 575; icteric index, 13.8; prothrombin time, 15 seconds; control, 15 seconds; cephalin flocculation, 1 plus in 48 hours; serum bilirubin, 2.23; thymol turbidity, 3.92 units; direct Van den Bergh, positive in 1 minute, indirect, 2.23. Urinalysis revealed a 1 plus albumin, a trace of urobilinogen in 1:100 dilution but no bile.

The patient appeared more dyspneic and weaker than on the previous day. Her temperature was 99° F.; pulse, 126; respirations, 36. She was seen by the civilian consultant who also agreed with the diagnosis. He advised frequent small transfusions until the blood picture showed improvement, a hysterotomy when her condition had improved, and a splenectomy either at that time or later. If, however, her condition showed no improvement, a splenectomy would then be indicated as an emergency measure. The consultant gave a very poor prognosis. She was then given 250 c.c. of whole blood slowly without reaction.

On Aug. 17, 1951, there was further evidence of cardiac failure. She was markedly dyspneic. The respirations were 38 and the cardiac rate 130 with a gallop rhythm. The liver was larger than on admission and presacral edema was present. She was immediately placed on continuous oxygen, given digitalis and 500 c.c. of packed red blood cells slowly.

At 5 P.M. the hematocrit was reported as 15. She had noted the onset of mild uterine contractions at approximately 3 P.M. At 5 P.M. contractions were recurring at 5 minute intervals, but lasting only 30 to 35 seconds. The cervix had effaced and softened considerably since the initial examination and had dilated 2 cm. The vertex was at the spines and the fetal heart-



beat was 140 in the right lower quadrant. She remained in the oxygen tent throughout labor and the blood transfusion was continued. Demerol, 75 mg., was administered at 7 P.M. A hematocrit at that time was reported as 18. At 9 P.M., under pudendal block, she was delivered spontaneously of a living premature male child, who weighed 2 pounds, 12 ounces. The total estimated blood loss was 75 c.c. She was sent to her room in fair condition and spent a restful night in the oxygen tent.

The patient was continued on digitoxin, folic acid, and vitamin B<sub>12</sub>. Throughout her hospital stay, typing and cross-matching were done on freshly drawn blood between each transfusion.

On Aug. 18, 1951, moderate improvement in her general condition was noted. Her temperature was 100° F.; pulse, 100; respirations, 30. She received 500 c.c. of whole blood without reaction. The hematocrit several hours later was recorded as 19. Prophylactic penicillin and terramycin were prescribed. The lochia was normal and the uterine fundus well contracted.

On August 19, the second postpartum day, her fever rose to 102.2° F. and she complained of moderately severe pain along the left costal margin anteriorly. The pulse was 108; respirations, 30. The chest was clear. The size of the liver and spleen was unchanged, but the spleen itself was quite tender. There was slight right costovertebral angle tenderness. The hematocrit was recorded at 22. A urine specimen, taken by catheter, revealed a 2 plus albumin, occasional white blood cells loaded with bacteria. The bile test was negative and urobilinogen test, positive, 1:140. Examination of the extremities was negative except for edema. The pain was relieved by 100 mg. of Demerol. A similar attack of pain occurred that evening, but was again relieved by Demerol. Daily transfusions were given in the next few days with gradual improvement in the blood picture. Despite intermittent episodes of left upper quadrant abdominal pain, the temperature gradually returned to normal. The spleen remained tender and enlarged and a friction rub was heard over the spleen. A diagnosis of splenic infarction was made.

By the tenth postpartum day the pain had almost disappeared. The blood picture revealed a red blood count of 4,100,000 and a hematocrit report of 45. She was able to move about the ward without ill effect. The liver had decreased in size and the spleen seemed slightly smaller and less tender.

The patient was seen by Dr. Nathan Rosenthal of New York on August 28. He confirmed our diagnosis and plan of therapy and suggested a splenectomy be done as soon as feasible. On September 2, the hematocrit reading was 42; red blood cells, 5,270,000; hemoglobin, 15.2 Gm. She was transferred to the Surgical Service where, on September 7, a splenectomy was performed through a left subcostal incision using gas oxygen, and ether endotracheal anesthesia. Multiple splenic infarcts, one of which was the size of a golfball, were noted. The etiology of these infarcts could not be ascertained. The postoperative course was uneventful.

Six weeks post partum she was completely free of complaints. The pelvis was normal. The baby weighed 5 pounds, 4 ounces, and was considered to be in good health. There was at that time no evidence of congenital hemolytic anemia in the child. The mother's blood picture was essentially within normal limits. Unfortunately, as is frequently the case with military personnel and their dependents, further follow-up was not possible.

CASE 2.—This 23-year-old white woman, gravida i, para 0, was first seen by us in the Prenatal Clinic at Fort Monmouth Army Hospital. She was approximately eight weeks pregnant at the time. Because of marked pallor, slight jaundice, and a palpably enlarged spleen she was admitted to the hospital for further study. The red cell count was 2,200,000; white cell count, 10,400; hemoglobin 8 Gm.; normal differential. Reticulocyte count was 7.2 per cent; platelets, 189,200; color index, 1.2; slight anisocytosis, poikilocytosis, and macrocytic cells were noted. The icteric index was 23.0 and the serologic test, negative. She was Rh positive. The hemogram was repeated and found to be essentially the same. The hematocrit was recorded at 22; direct bilirubin was positive; the indirect was 2.8 mg. per 100 c.c. The bleeding and clotting times were normal. The urine was negative for bile, but the urobilinogen

was positive in dilutions up to 1:10; the cold agglutinins test was negative. The indirect Coombs test was negative. A fragility test was reported as follows: In the control, hemolysis began at 0.42 and ended at 0.33; in the patient hemolysis began at 0.51 and ended at 0.33.

On the basis of these findings a tentative diagnosis of hemolytic anemia, probably congenital in type, was made. In order that the patient might be with her husband during her pregnancy and illness, she was transferred to Walter Reed Army Hospital.

Review of the patient's past history revealed that at the age of 7 she had been admitted to the James Whitcomb Riley Hospital in Indianapolis, Indiana, because of lobar pneumonia and diphtheria. Marked pallor and jaundice of the skin and scleras had been noted. A diagnosis of idiopathic hemolytic anemia was made and several transfusions administered. She was readmitted two to three months later for a splenectomy. Examination of all available relatives failed to reveal any hemolytic tendency. Since the patient herself was markedly improved, the splenectomy was deferred and the patient discharged and advised to take vitamins and iron. Again at the age of 17 she had been treated for anemia with vitamins and iron and the blood count had reverted to normal.

The family history and system review were not significant. Physical examination revealed the patient to be well developed, well nourished, and in no acute distress. Her weight was 146 pounds; her pulse was 104, and blood pressure, 124/60. There was a Grade II physiologic systolic murmur at the base of the heart and an inconstant reduplication of the second sound at the apex. The uterus was palpable midway between the umbilicus and the symphysis pubis. The spleen was palpable 3 cm. below the left costal margin. Pelvic measurements were within normal limits.

Laboratory work on admission revealed a red blood count of 1,700,000 with 7.2 Gm. of hemoglobin. The white blood cell count, differential, platelet count, prothrombin time, and coagulation time were within normal limits. The hematocrit was recorded at 24. The total protein and albumin/globulin ratio were also normal. During the hospital admission some 100 different laboratory procedures were performed. The platelet counts, except for a slight increase following splenectomy, were within normal limits. The white count was also normal except for a very slight increase following splenectomy. There was a constant elevation of the serum bilirubin. The reticulocyte count and general blood picture showed no appreciable change after the administration of iron, liver extracts, folic acid, or vitamin B<sub>12</sub>. Bone marrow aspiration of the sternum obtained on April 3, 1951, was compatible with hemolytic anemia. Fragility tests were done repeatedly during hospitalization and were normal at all times despite the report from the Fort Monmouth Hospital that tests there revealed increased fragility. An x-ray examination of the abdomen on April 7, 1951, revealed an enlargement of the spleen and liver. Chest x-rays were normal.

During this hospital admission consultations were held several times with three different civilian consultants in hematology. The consensus, after thorough evaluation, was that this patient might have congenital hemolytic anemia without spherocytosis despite the absence of a good familial history. It was agreed that a splenectomy should be done, although it might not be of value.

Multiple transfusions were administered without reaction and the patient prepared for a transthoracic splenectomy which was performed on May 16, 1951. The postoperative course was uneventful. The pathological diagnosis was given as passive congestion of the spleen. She was discharged to the care of the Obstetrical and Medical Out Patient Sections on June 13, 1951.

She was seen at frequent intervals as an outpatient, and appeared to be doing well even though the splenectomy did not result in complete cessation of the hemolytic process, but served only to reduce its severity. She was readmitted on Aug. 21, 1951, for further observation. At that time the red cell count was 3,200,000 with 64 per cent hemoglobin; the platelet count, 1,600,000; the reticulocyte count, 31 per cent; sickling test, negative; urine bile 2 plus; serum bilirubin, 2.3; Van den Bergh, direct 0.4, indirect 1.9; and the red-cell fragility test was within normal limits.

She remained in the hospital for 36 days, during which time she was essentially afebrile and asymptomatic. The purpose of her rather prolonged hospital stay was to provide ade-

quate prompt therapy in the event she might develop an acute hemolytic crisis. It was felt that the hematocrit recording should, if possible, be maintained at 35 or better. The definite cause for the patient's continued jaundice and anemia could not be determined nor could the reason for her continued hemolysis. She received approximately 2,500 c.c. of whole blood. A slow rise to 36 in the hematocrit was noted and a moderate progressive drop in the serum bilirubin from 6.6 to 4.0 with a direct Van den Bergh of 2.2, and an indirect of 1.8. There was a clinical clearing of the patient's jaundice and she appeared subjectively improved and stronger. She was discharged on Sept. 26, 1951.

The patient was readmitted on Sept. 28, 1951, in active labor and, without complication, was delivered of a living normal 8 pound, 12 ounce girl. Prior to delivery the hematocrit was reported at 35 and the Van den Bergh at 6.6. Following delivery the hematocrit registered 38, the Van den Bergh was 1.7: direct, 1.0, indirect, 0.7. Within a few days there was a marked decrease in the clinical jaundice and she was discharged to the Out Patient Department on Oct. 3, 1952.

Since then she has been followed as an outpatient by the Medical Service and Gynecology Section and has remained essentially symptom free. She was last seen on May 16, 1952. The last recorded hemogram revealed a hematocrit of 35 with a red cell count of 3,650,000 and a white cell count of 12,400 with a normal differential. Since that time her husband has been discharged from the service and no further follow-up has been possible.

### Comment

Two cases of hemolytic anemia associated with pregnancy have been presented. One case was congenital, the other must be classified as idiopathic. Only 10 similar cases have been reported in the literature. It is somewhat presumptive, therefore, to formulate any dogmatic principles of etiology and management on the basis of such a limited series.

It has been pointed out earlier in this article that pregnancy is apparently a precipitating factor in the occurrence of a hemolytic crisis. Hemolytic anemia does not alter the fertility or menstrual cycle. The incidence of miscarriage, antepartum or postpartum hemorrhage, or other obstetrical complications is not increased by the disease. There is no indication for termination of pregnancy. A successful outcome of the pregnancy can be expected and succeeding pregnancies should be uneventful.

In approximately 30 per cent of the reported cases a conservative course of management was followed. Multiple transfusions and supportive therapy were successfully given. It has long been the contention of those who have studied hemolytic anemia that transfusion may precipitate a further crisis. However, in none of the cases reviewed was this encountered. Great care should be taken in cross-matching each and every unit of blood and freshly drawn blood should be used for this purpose.

When hemolytic anemia is encountered in the first and second trimesters, multiple transfusions should be given slowly and cautiously until a satisfactory hemogram is obtained. A splenectomy should then be performed, together with a thorough search for accessory spleens. The transthoracic approach is preferable, since unnecessary trauma to the abdominal cavity and its contents, including the gravid uterus, can thus be avoided. If the disease is encountered in the third trimester, conservative management until delivery is advised, and the method of delivery should be governed by obstetrical indications. The transthoracic splenectomy should be performed early in the puerperium in order to hasten the patient's complete recovery.

### Summary

Two cases of hemolytic anemia associated with pregnancy are added to the literature. The first patient was treated conservatively and the second by splenectomy.

In the first and second trimesters, a transthoracic splenectomy is suggested. A conservative approach should be followed, if possible, if the disease is encountered in the third trimester.

Hemolytic crises were not encountered in either case when whole blood was administered to the patients.

Obstetrical complications were not increased by the presence of hemolytic anemia. The method of delivery should be governed by obstetrical indications only.

The infant apparently is not affected by the disease in a well-managed case. However, the congenital tendency of the disease is well known. A careful follow-up of both mother and infant is, therefore, imperative.

Since hemolytic anemia associated with pregnancy is quite rare and its mode of therapy not well established, all such cases should be reported by the profession.

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## Department of Case Reports New Instruments, Etc.

### THE REDUCTION OF THE ANTI-RH ANTIBODY TITER BY CORTISONE ADMINISTERED DURING PREGNANCY

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ATTEMPTS in the past to modify the course of hemolytic anemia of the newborn due to Rh incompatibility have met with failure. Following the discovery of the effectiveness of cortisone in acquired hemolytic anemia,<sup>1</sup> a new rationale for the prevention of hemolytic anemia of the newborn seemed plausible. Doerner<sup>2</sup> found it of little value when administered during the last 2 months of pregnancy. However, prior to this latter report we<sup>3</sup> successfully treated a patient for an acquired hemolytic anemia throughout her entire pregnancy with cortisone and corticotropin. The favorable hematologic response together with the delivery of a normal child led us to administer cortisone during the last 6 months of pregnancy to a patient with a markedly elevated anti-Rh antibody titer. The effect of this therapy, on both the mother and child, is reported.

Mrs. L., a 26-year-Negro woman, gravida iii, para ii, was found to be 3 months pregnant in February, 1952. Her first pregnancy in 1947 was entirely normal. Her second child died 4 hours after birth in 1950 because of hemolytic anemia of the newborn. Blood typing at this time revealed the father to be A<sub>1</sub>CDE/cDE; the mother was A<sub>1</sub>cde/cde. The anti-Rh antibody titer was 1:512 in albumin and 1:64 in saline. After explaining the poor prognosis as regards a living baby, oral cortisone therapy was begun. With an average daily dose of 50 mg., the anti-Rh antibody titer in saline disappeared completely, while that in albumin fell as low as 1:8, only to rise slightly before delivery. The indirect Coombs test remained unaffected, however (Table I).

The patient was kept on a salt-poor diet. No clinical signs of hypercorticism, i.e., edema, acne, glycosuria, or hypertension, were seen. The entire pregnancy was completely uneventful and on July 7, 1952, a normal, spontaneous delivery occurred.

TABLE I. ANTIBODY RESPONSE TO CORTISONE

DATE	GESTATION (MONTH)	ANTI-Rh ANTIBODY TITER		INDIRECT COOMBS' TEST	CORTISONE (MG./DAY)
		ALBUMIN	SALINE		
2/26/52	3	1:512	1:64	1:64	100/3 days
3/14/52	4	1:256	1:64		50
3/21/52		1:128	1:16		↓
4/ 4/52	5	1:32	1:8	1:64	25
					↓
4/25/52		1:16	1:8		50
5/ 2/52	6	1:32	1:4	1:64	
5/16/52		1:16	1:4		↓
5/28/52		1:8	--	1:256	
6/13/52	7	1:16	--		↓
6/27/52		1:16	--		75
7/10/52	8½	1:32	--	1:128	↓ (delivery)

The child weighed 5 pounds, 9 ounces. Pallor of the mucous membranes was noted. Scleral icterus soon developed. The liver and spleen were palpable at the level of the umbilicus. Hydrops or developmental abnormalities were not seen. The placenta weighed 455 grams and appeared slightly edematous.

The cord blood showed: red blood count 1.54 million, hemoglobin 7.7 Gm. (50 per cent), reticulocytes 92 per cent, white blood count 12,800 with 8 per cent metamyelocytes, 4 per cent segmented cells, 88 per cent lymphocytes; 950 nucleated red blood cells per 100 white blood cells were counted. The Coombs test was positive. The cord serum bilirubin was 3 mg. per cent direct, and 6.1 mg. per cent indirect.

A diagnosis of hemolytic anemia of the newborn was made at birth and an exchange transfusion begun. The child died 2 hours later and before the exchange transfusion could be completed. The characteristic findings of extramedullary hematopoiesis in the liver and spleen were present. The lymph nodes and adrenals appeared normal. Kernicterus was not present and no developmental anomalies were seen.

### Comment

The effectiveness of cortisone in markedly reducing the anti-Rh antibody titer during pregnancy was clearly demonstrated in this patient. The indirect Coombs titer remained unchanged despite the falling antibody titer. This was reflected in the failure to prevent hemolytic anemia of the newborn in this instance. It is suggested that the indirect Coombs test and titrations should be done in all instances where attempts are made to modify the antibody production. The absence of abortion, kernicterus, and hydrops was most heartening in view of the high antibody titer early in pregnancy.

The failure to prevent hemolytic anemia of the newborn was due to incomplete suppression of antibodies in the mother's serum. This suggests that the institution of higher doses of cortisone *early* in pregnancy may be effective. The importance of a salt-poor diet to prevent fluid retention and hypertension must be emphasized.

The contraindications to cortisone therapy must be borne in mind. Evidence of tuberculosis, peptic ulcer, ulcerative colitis, diabetes, psychoses, or severe hypertension contraindicates such therapy. The advisability of routine administration of cortisone to all pregnant women with anti-Rh antibodies in the serum is still to be determined. The encouraging results seen in our patient suggest the need of further clinical investigative trial.

### Summary

1. The effectiveness of cortisone in reducing the anti-Rh antibody titer during pregnancy is discussed.
2. The contraindications to such therapy are mentioned.

We wish to thank Dr. Helene O. Dickens for permitting us to report the findings in her patient. Dr. Elmer Alpert of Merck & Co., furnished the cortisone for this investigation.

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## PREGNANCY AND VAGINAL DELIVERY FOLLOWING RADICAL SURGERY FOR CANCER OF THE VULVA

### Review of the Literature and Case Report

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PARTURITION following radical vulvectomy for malignancy is extremely rare. Among 2,864 cases of radical vulvectomy which have been reported, subsequent pregnancy was mentioned for only 4 patients. Delivery was by the vaginal route in only one. This occurred in a 27-year-old woman who had vaginal deliveries six and nine years after a radical vulvectomy.<sup>1</sup> The remaining 3 patients were subjected to cesarean section. One was a 28-year-old woman on whom Way<sup>2</sup> did a radical operation for vulvar carcinoma. Two and again five years later "successful" pregnancies were terminated by lower segment cesarean. Way also cited a personal communication from W. F. T. Haultain, who "has encountered a case necessitating cesarean section." Collins<sup>3</sup> reported the case of a 33-year-old woman who was delivered by cesarean. In the above cases information is lacking as to the patients' parity, the extent of vaginal scarring, and the size of subsequent infants.

The present report deals with a patient who was delivered vaginally fifteen months after a radical vulvectomy. The case is reported not only because of its rarity but also to add information on the obstetrical management of such patients and on the effects of pregnancy on their malignancy follow-up histories.

### Case History

Mrs. E. R., a 37-year-old Negro para i, gravida iii, was admitted to the Gynecologic Service of the University of Pennsylvania Hospital Aug. 1, 1950, with a chief complaint of right vulvar pain. An ulcer had been noted on the right labium majus for six months. In June, 1950, she had been treated on the Dermatologic Service for congenital syphilis. At that time a portion of the labial lesion removed for biopsy showed noninvasive epithelioma.

The past medical history was negative except for a hemorrhoidectomy in 1942, a full-term delivery in 1930, a miscarriage in 1928 at six months, and another miscarriage (triplets) in 1937 at five months.

Physical examination revealed a tender, slightly ulcerated, flat lesion, 2 cm. in diameter, in the middle of the right labium majus. No inguinal nodes were palpable. There was x-ray evidence of old pulmonary tuberculosis in the right lung. The patient was otherwise healthy.

On Aug. 2, 1950, the lesion was completely excised with 1 cm. of surrounding skin and a small amount of subcutaneous tissue. Microscopic examinations revealed invasive squamous-cell epithelioma (Fig. 1).

A radical vulvectomy and Basset type lymphadenectomy were performed on Aug. 16, 1950. Lymph nodes were removed from both femoral triangles, the inguinal areas, and the region of the external, internal, and common iliac vessels. The skin overlying the area of node dissection on the right side was removed in continuity with the vulva.

Neither the 16 nodes obtained from the right side, nor the 15 nodes removed from the left side contained microscopic evidence of cancer. Skin defects which could not be closed primarily were covered with split-thickness skin grafts from the abdomen. Wound infection resulted in loss of some of the grafts. On the twenty-second postoperative day the wound appeared clean, and granulations were present. A second skin grafting resulted in an 80 per cent successful growth. Eighteen days following this procedure, the patient was discharged.

Follow-up examinations revealed dense scar formation, especially over the perineal body area, and the region between the vulvectomy and the site of the node dissection on the right. There was brawny edema of both legs from the toes to the hips.



Fig. 1.—Photomicrograph of section from the right labium majus showing stromal invasion by squamous-cell epithelioma. ( $\times 200$ .)

On May 29, 1951, nine months after the radical vulvectomy, the patient reported that she had last menstruated Feb. 26, 1951. Examination revealed extensive keloid formation in the right groin. The edema of the legs was unchanged. The vagina admitted two fingers, but the introital and peri-introital tissues were densely scarred. The cervix had a healed, stellate laceration. The uterus was soft and enlarged to the size of a twelve weeks' gestation. The adnexa were normal.

The patient had an uneventful antepartum course. The edema of the legs did not increase. On Nov. 20, 1951, in the thirty-sixth week of pregnancy, the membranes ruptured spontaneously, and she went into labor 10 hours later. After a seven-hour labor, she was delivered spontaneously, under nitrous oxide-oxygen anesthesia, of a 2,190 gram (4 pounds, 13 $\frac{1}{4}$  ounces) female infant in good condition. An episiotomy was not required, and there were no maternal lacerations. No cause for the prematurity could be ascertained. After an uneventful postpartum course, mother and infant were discharged in good condition on the sixth postpartum day.

When last seen on Dec. 11, 1952, thirteen months postpartum, the patient was in good health, except for brawny edema of both legs extending up to mid-thigh. There was no evidence of recurrence of the malignancy. The infant was healthy and weighed 25 pounds.



*Comment.*—The rarity of pregnancy following radical vulvectomy can be largely explained by the fact that vulvar malignancy occurs predominantly in patients beyond the reproductive age. For all reported cases of radical vulvectomy, the average patient age (where given) at the time of treatment was 60.7 years. Even if the individual is within the reproductive era, vaginal cicatrization may discourage or prevent coitus. In an occasional patient, pelvic irradiation used as a supplement to surgical treatment may decrease or destroy fertility.

When the present patient was first seen in the third month of pregnancy, the scar tissue was so extensive and firm that vaginal delivery at term appeared impossible. Five months later, when spontaneous labor began during the thirty-sixth week, the tissues had softened enough to permit normal delivery. It appeared likely that a full-term vaginal delivery would have been feasible.

The available information on the four previously reported patients gives no indication that pregnancy produced deleterious effects as far as their previous cancer was concerned. Our patient has also remained healthy.

### Summary

The literature on pregnancy and delivery following radical surgery for vulvar malignancy is reviewed. Of 2,864 reported cases of radical vulvectomy, subsequent pregnancy is mentioned for only four patients. Three of the four were delivered by cesarean section. The fourth was delivered vaginally six and nine years after operation.

An additional patient who had a vaginal delivery is reported, and the factors which influenced her management are presented.

Pregnancy exerted no apparent deleterious effects as far as the previous malignancy was concerned.

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## PRIMARY ENDOMETRIOSIS OF THE CERVIX

LEONARD ZWEIBEL, M.D., NEWARK, N. J.

(From Newark Beth Israel Hospital)

ONE of the earliest notes of progress in this century's renaissance era of gynecology is the term endometriosis, which was introduced by Sampson in 1912 to include a wide variety of adenomatous lesions of the female pelvis, the histological and functional characteristics of which are identical with those of the endometrium. The lesion may contain endometrial stroma with or without glands, outside of the normal endometrial site, some of which respond physiologically to the stimulus of menstruation and the changes of pregnancy. The stroma is the aggressive part and is followed by the glands. There are two types:

1. *Orthotopic*.—That which arises in continuity with the mucosal lining of the derivatives of the Müllerian duct; in the uterine wall the lesions are called adenomyosis or internal endometriosis.

2. *Ectopic*.—That which is called true endometriosis. The condition was recognized, but not well understood, late in the nineteenth century. The lesion is often associated with endometrial hyperplasia and with leiomyomas. It occurs in the reproductive life, usually between the ages of 30 and 40 years. The symptomatology is not unlike that found in pelvic inflammatory disease.

The lesions of endometriosis occur in the following important regions in this general order of frequency: (1) the myometrium; (2) the ovary; (3) the cul-de-sac of Douglas, involving the uterosacral ligaments and/or infiltrating through the posterior vaginal vault and extending onto the cervix. This is the most common involvement of the cervix. Isolated lesions of the cervix per se are very rare and reports in the literature would bring the total to less than one dozen, none of which were diagnosed prior to surgery. Other locations, more common than that of the cervix, are in abdominal scars, umbilicus, appendix, round ligament, inguinal canal, and bladder. Occasionally some portion of the intestinal tract is involved in this disease, often a lesion of the rectosigmoid or terminal ileum has been seen, as well as in remote parts of the body such as in the lungs.

As stated previously, endometriosis of the cervix per se, whether or not accompanied by separate lesions elsewhere, has been rarely recorded. The cervical lesions may fit in with Sampson's theory of direct implantations or with the theory of Robert Meyer that the lesions rise from celomic epithelium, arising in situ from heteroplasia. Frank described adenomatous growths of the cervix as derivatives from Gartner's duct. However, this embryonic tissue lends itself to Gartner's duct cysts, occurring on the lateral areas of the cervix and vagina. Novak mentions endometrial development in the cervix, in a number of instances, but does not specify whether these are isolated lesions, or the more common extensions from the cul-de-sac.

The gross characteristics of isolated cervical endometriosis are that the lesions usually have the appearance of small superficial islands or implants of endometrial tissue, pin-point to pea size, although chocolate cysts may grow, the latter to the size of a lemon, as reported in one case.

### Case Report

Mrs. I. L., a 31-year-old white woman, para ii, gravida ii, was seen April 5, 1952, complaining of menorrhagia, with small clots, since the birth of her second child 22 months prior to her visit. She had had menometrorrhagia since her last menses on March 24, 1952,

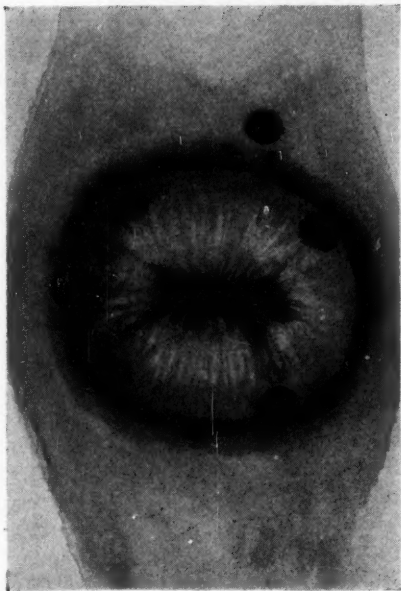


Fig. 1.

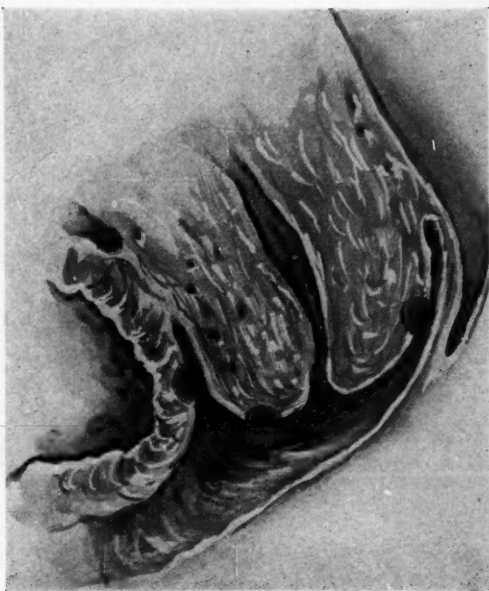


Fig. 2.



Fig. 3.

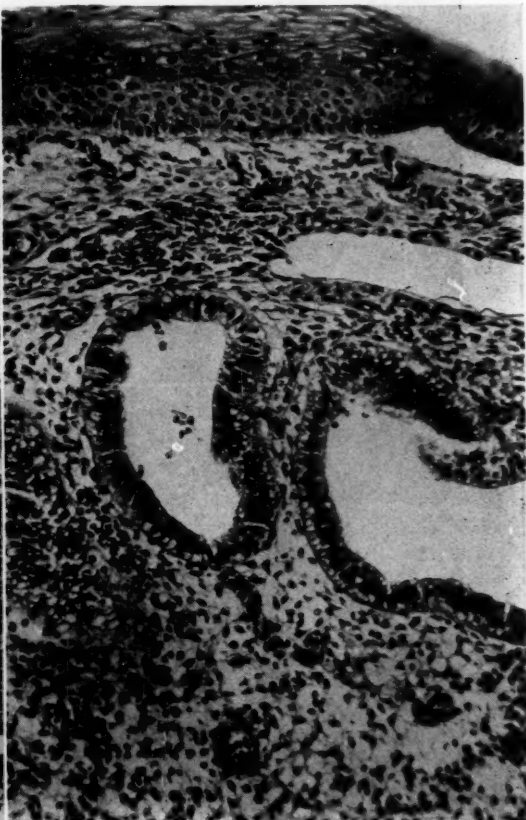


Fig. 4.

Fig. 3.—Section of cervix showing endometrial glands and stroma beneath stratified squamous epithelium. (Hematoxylin and eosin.  $\times 40$ .)

Fig. 4.—Higher power of the same section showing details of glands and stroma. Note subnuclear vacuoles of early secretory phase. (Hematoxylin and eosin.  $\times 170$ .)

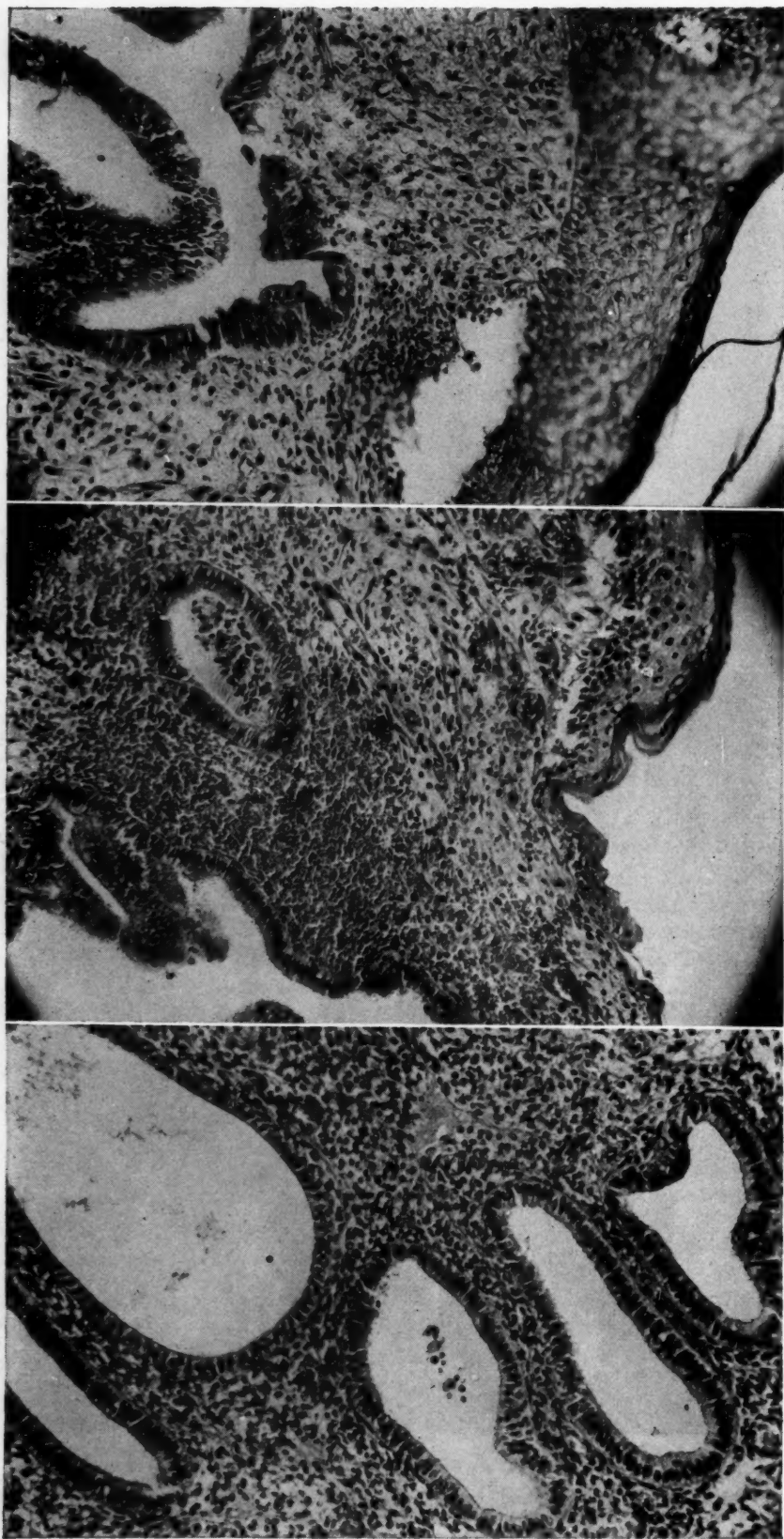


Fig. 5.

Fig. 5.—Another area showing additional features of endometrial glands and stroma. (Hematoxylin and eosin.  $\times 170$ .)  
 Fig. 6.—Another field. Gland lumen contains desquamated epithelial cells.  
 Fig. 7.—Consists of cervical tissue and shows beneath the epithelium a single tortuous gland of endometrial type surrounded by character-

Fig. 6.

Fig. 7.

istic stroma. There is slight hemorrhage into the stroma.



associated with lower backache and right lower quadrant pain. There was no nausea or vomiting. Menstrual periods began at the age of 12, were regular every 28 days, lasting 6 to 7 days, the flow moderate the first 2 days with no clots and only slight lower abdominal pain throughout, not progressive. The first pregnancy was normal 5 years previously. The second had been complicated by hypertension. Both deliveries had been normal.

Physical examination showed the patient to be moderately obese, weight 159¼ pounds, height 64 inches, with pulse 60, and blood pressure 138/84. The head was normal; the thyroid uniformly slightly enlarged, no bruits. Lung sounds were normal. The heart rate was slow, with many extrasystoles, no bruits. The breasts were pendulous, no masses palpable. The abdomen had no masses or rigidity. There was moderate tenderness over the pylorus. Knee reflexes were normal.

Pelvic examination revealed a parous introitus, the anterior vaginal wall intact. There was slight rectocele. The cervix was posterior showing five hemorrhagic mottled grayish and white nodules, 3 to 5 mm. in diameter, four at the junction of the vaginal mucosa and cervix at 2, 5, 9, and 10:30 o'clock, and one lesion about 2 cm. above the cervix on the anterior vaginal wall between 12 and 1 o'clock (Figs. 1 and 2). The uterus was anterior, slightly irregular and boggy, the size of an 8 weeks' gestation. The adnexa and parametria were negative.

The impression was primary endometriosis of the cervix and endometrial polyposis.

Mrs. I. L. was operated on at Newark Beth Israel Hospital on April 11, 1952. All nodules were removed and the bases cauterized with actual cautery. Curettage was performed with removal of profuse amounts of hyperplastic endometrium, much of which resembled polyps. The postoperative course was uneventful and the patient was discharged April 14, 1952. She was advised to balance her diet and reduce her weight. Postoperatively the lesions were treated with silver nitrate.

The patient was seen on June 26, 1952; her weight was 137½ pounds and her only complaint was spotting. On examination there was a new lesion only about 2 mm. in diameter, oozing blood. This area was cauterized on the posterior vaginal wall at the very angle of the cul-de-sac. This lesion may have been smaller and not seen at the time of the operative procedure. The cervix was clean and the uterus anterior, firm, and normal in size. Menses since hospitalization have been free of symptoms. On July 3, 1952, the cauterized area was healed and there was no more spotting. The patient was advised to try for another pregnancy with the hope that this would lessen the tendency to recurrences of endometriosis.

On Oct. 3, 1952, follow-up showed three more 3 mm. lesions on the cervix. These were removed and sent to the laboratory.

*Pathologic Report.*—(70073A Microscopic, April 11, 1952.) The four fragments consisted of cervical tissue covered in part by stratified squamous epithelium. In three of the four fragments beneath the epithelium there were groups of rather tortuous irregular glands lined by pseudostratified columnar epithelium, containing secretion vacuoles, both sub- and supranuclear. The epithelium rested on a thin but distinct basement membrane. These glands rested within a cellular stroma made up of small spindle cells. Both glands and stroma were characteristically endometrial. The phase was distinctly late proliferative to early secretory. The stroma was vascular and hemorrhagic. The blood vessels were thin-walled capillaries. This stroma was distinct from the less cellular cervical stroma. There was a mild inflammatory infiltrate in and about the endometrial tissue. The fourth fragment contained a hemorrhagic area in which there appeared to be some endometrial stroma but no glands.

## PARASITIC FIBROID

SIMON BRODY, M.D., BROOKLYN, N. Y.

(From the Williamsburgh General Hospital)

THE problem of parasitic myomas attracted a great deal of attention in the early part of the century and much was written about it in the literature at the time. There is hardly any mention of this condition in recent or current literature. This may be due to the fact that fibroids are at present recognized and operated on comparatively early and there is, consequently, but little chance for any of them to become completely detached from the uterus. Then, again, it is possible that the finding of parasitic or wandering myomas is quite common and no great significance is attached to it.

According to Kelly and Cullen,<sup>1</sup> myomas that have for some reason become partially or almost completely separated from the uterus and receive their main blood supply from another source may be termed parasitic. This other source of nourishment may be the omentum, the Fallopian tubes, the mesenteric vessels, the large or small intestines, the bladder, the abdominal wall, the broad ligament, or several of these sources at the same time. Of these, the most frequent source of blood supply is the omentum. In many cases where myomas exist the omental adhesions are associated with dense pelvic adhesions or with pus tubes. Here it is perfectly natural that the omentum should become firmly adherent. Of special interest are those cases in which the tubes and ovaries are comparatively normal, yet the omentum becomes adherent to the subperitoneal and usually pedunculated nodules and soon furnishes a large part of their nourishment. The cause of this phenomenon seems to be inherent in the myomas and not in the surrounding organs. It is well known that myomas have a diminished blood supply, especially the pedunculated ones. Owing to this diminished blood supply, the myomas are usually prone to degenerate and often show hyaline degeneration and necrosis. The peritoneal surface develops a slight roughening and the omentum at once becomes adherent.

Thirty-seven cases were reported by Kelly and Cullen.<sup>1</sup> In all of them, except one, the parasitic fibroid was attached to the uterus and received its additional nourishment, to a varying degree, from another organ, most frequently the omentum. In only one case was the myoma entirely separated from the uterus, being attached to and enveloped by the omentum, which, however, was also adherent to the uterus and the right tube and ovary.

R. Peterson<sup>2</sup> reported twenty cases of migratory fibroids collected from the literature and three cases of his own, a great number of which were entirely detached from the uterus. Some of these were discovered only upon autopsy. More recently, Frank<sup>3</sup> described a large fibroid weighing 12 pounds which had no connection with the uterus and was nourished by the large omentum.

The case of a parasitic fibroid described here presents some interesting clinical and pathological features to justify the reporting of it in the literature.

### Case Report

R. G., a 31-year-old white woman, was admitted to the hospital on Feb. 25, 1952, complaining of pain in the abdomen of two days' duration. The pain was in the epigastric region radiating to the lower abdomen. It was constant and was aggravated upon standing or bending down. There was no history of vomiting and no vaginal staining. The patient complained of some pain on urination. She was a gravida i, para i, with a child 6 months old. The last menstrual period occurred two weeks prior to her admission to the hospital.

The physical examination revealed a fairly well-nourished woman appearing acutely ill. Her temperature was 99.4° F., pulse 88 per minute, and respirations 20. The blood pressure was 110/70. The heart and lungs were negative. There was marked tenderness, rigidity, and peritoneal rebound over the lower abdomen, most pronounced over the left lower quadrant. Vaginal examination revealed the cervix to be high, closed, and very tender. The uterus was normal in size and retroposed. In front and above the body of the uterus, and separated from it, there was a mass about 7 cm. in diameter. It was cystic, movable, and extremely tender. No other masses were palpable. The blood count showed hemoglobin 12.4 Gm., red blood count 4.2 million, white blood count 8,600 with 82 per cent polymorphonuclear leukocytes, 4 per cent monocytes, 12 per cent lymphocytes, and 2 per cent eosinophils. The urine was essentially negative.



Fig. 1.—Parasitic fibroid and part of greater omentum. Note the blood vessels going from the omentum to the fibroid and the thin pedicle, as well as the hemorrhage in the portion of the tumor adjacent to the pedicle.

A provisional diagnosis of twisted ovarian cyst was made and immediate laparotomy was performed. When the peritoneal cavity was entered the tumor was easily found but it felt very loose, floating in the abdomen. It was brought out through the wound and found to be attached to the large omentum by a thin pedicle and a few blood vessels. It was twisted on its pedicle two and one-half times. It was 8 cm. in diameter, hard and edematous. Upon further examination a short threadlike cord was found attached to the tumor at a point diametrically opposite to the point of its attachment to the omentum. It was 0.5 cm. long and its loose end appeared freshly torn. While it was being handled, this little appendage became separated from the tumor. The uterus was normal in size and regular in outline. There were no fibroids visible or palpable in the body of the uterus. At the upper central aspect of the fundus uteri there was a raw surface in the serosa about 2 mm. in diameter. This was apparently the spot at which the tumor was attached to the uterus by a threadlike structure found on the former. This very thin pedicle was

probably severed during the delivery of the tumor into the abdominal wound. The tumor was removed by clamping, tying, and cutting the portion of the omentum to which it was attached. The patient made an uneventful recovery and was discharged on the ninth postoperative day in good condition.

The pathological diagnosis as given by Dr. Aaron Coblenz follows:

*Gross.*—The specimen consisted of: (1) minute fragments of grayish tissue measuring 3 mm. in greatest diameter, (2) a discrete oval nodule of tissue measuring 8 by 6 cm. The outer surface was smooth except in one area where a segment of omental fat measuring 13 by 5 cm. was attached. A pedicle connected the capsule of the nodule with the omental fat and this pedicle was twisted with a marked hemorrhage of the adjacent tissue as well as of the pedicle. The hemorrhage extended to the surface of the nodule, covering large areas of it (Fig. 1). On section the nodule had a fibrous consistency and was composed of a grayish-white tissue in whorled arrangement which, however, had undergone grayish-pink degeneration with softening of the central portions. It appeared to be delimited by a thin connective tissue capsule. Near the pedicle there was a large area of hemorrhage which measured up to 1 cm. in thickness.

*Microscopic.*—(1) The specimen was apparently composed of material which disintegrated during processing. (2) Microsection through the large mass revealed that it was composed of a homogenous pink-staining material which contained no viable cellular elements. However, shadows of cells were noted and the general architecture was characteristic of a fibroleiomyoma. There were large areas of calcification and on the periphery there was extensive hemorrhage.

*Diagnosis.*—Parasitic fibroleiomyoma with strangulation and necrosis.

### Summary and Conclusions

A case of parasitic fibroid is reported. It was a solitary tumor measuring 8 by 6 cm., attached to the great omentum by a short pedicle and a few blood vessels. These omental blood vessels constituted the sole nourishment of the myoma. The tumor was attached to the fundus of the uterus by a short (0.5 cm. long) attenuated, threadlike pedicle. This was severed at the uterine end during the attempt to deliver the tumor into the abdominal wound. The uterus was normal in size and contained no other myomas. The existence of the tumor remained unsuspected until it became twisted on its omental pedicle giving rise to acute symptoms and clinical findings necessitating immediate surgical interference.

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642 EASTERN PARKWAY  
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# Editorial

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## Society of University Gynecologists

The editors wish to take this opportunity to give a nod of approbation upon the formation of the Society of University Gynecologists. This youngest of organizations in our specialty is dedicated to the encouragement of fundamental research and teaching in the field of human reproduction.

Recently a number of academic departments in obstetrics and gynecology have come under the leadership of relatively young men who have been well trained in the concepts of basic research. These men have felt a lack of opportunity for free interchange of ideas, not only among themselves but with interested nonclinical personnel. They have also been deeply concerned with the validity and worth of their teaching methods and their abilities to encourage other young men to take up this field of endeavor. The Society is formed to fill this void and is in no sense a retreat to the "ivory tower" nor is it the intent of the members to foster exclusiveness. Rather it is an effort by individuals with certain common problems concerning both research and pedagogy to meet for a free and informal exchange of ideas.

Although the word "gynecology" appears in the Society's name, it is the expressed intent of the charter members that the rolls of the Society be open to all those of academic standing whose interests are devoted to research in any aspect of human reproduction. The emphasis is definitely on youth and some rather unique efforts have been made to ensure continued academic interests and achievement on the part of the members.

The first meeting of this Society is to be held in Cincinnati in December. The concepts of this organization are worthy. Its ideals are high. The editors therefore take this opportunity to welcome it to the roster of obstetrical and gynecological societies; to wish it a long and active life; and to hope that from such interchange of thought will come not only advancement in research in this specialty but progress in its teaching. Godspeed.

*The Editors.*

# Department of Reviews and Abstracts

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CONDUCTED BY GEORGE W. KOSMAK, M.D., NEW YORK

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## Selected Abstracts

### Anatomy, Anomalies

**Bernard, Robert M.:** *The Shape and Size of the Female Pelvis*, Edinburgh M. J. 2: 29, 1952.

Bernard's thesis in this article is that there is a definite relationship between the over-all height of a patient and the configuration of her pelvis. He also feels that there is a definite further relationship between height, environmental influences, and pelvic shape. The difference in incidence of round pelvis in relation to the tall and small women is of no statistical significance; however, the difference in incidence of flat pelvis in these two groups of women is statistically significant. The study further shows that the distribution of small and tall women according to "social class" is significant. There is a greater proportion of tall women in social Classes 1 and 2 than there is in Classes 3, 4, and 5.

The author presents an index for the brim and a combination index for the brim. These are additional statistics to be calculated. He hopes from the calculation of these statistics to be able to predict pelvic dystocia. The information given by these indices is already supplied by the study of the roentgenograms, and like similar indices serve no real function in the understanding of pelvic mensuration or configuration.

He suggests rather emphatically that the determination of pelvic configuration by hormonal influences is probably of less importance than is environment. He shows quite clearly that in 100 male pelvises (medical students) the incidence of "android" pelvis is of approximately the same order as it is in 100 women of social Classes 1 and 2. That is to say, the so-called "android" pelvis is not the typical male pelvis, because 80 per cent of the medical students examined had round pelvises. This latter part of the study is most interesting.

The author therefore concludes that environmental factors are of great importance in influencing the shape of the pelvis. He also concludes that the relationship existing between tall women and good pelvises and short women and poor pelvises is indirectly a relationship of environmental or economic status. The lower economic groups have fewer tall women and therefore fewer good pelvises.

This work is most interesting and certainly is entitled to consideration by obstetricians and gynecologists interested in the study of the pelvis. L. M. HELLMAN.

### Anesthesia, Analgesia

**Freeth, Derek, and MacVine, J. S.:** *The Value of External Cephalic Version Under Anaesthesia*, Brit. M. J. 2: 881, Oct. 13, 1951.

The author briefly reviews the results reported in the literature concerning external version employing anesthesia. In addition, a statement is made regarding the usual fetal loss in breech delivery. The purpose of the study was to determine if the results obtained in routine external version under anesthesia justified the recommendation of its use. The

contraindications are stated to be multiple pregnancy, suspected placenta previa, toxemia (including hypertension), previous classical cesarean section, and cases elected to be delivered by cesarean section regardless of the presenting part. The actual technique is described. The procedure was carried out on 214 patients, after unsuccessful attempt at external version without anesthesia. There were 11 fetal deaths, of which 3 were attributable to the version, giving a mortality of 1.4 per cent. All of these deaths occurred in parous women. These cases in which fetal loss occurred are discussed in detail. The maneuver was successful in 81.3 per cent of the cases. The author concluded that the number of successes, together with the low fetal risk, justifies the adoption of the procedure as a routine antenatal measure.

DONALD G. JOHNSON.

### Cancer, Malignancies

**Evans, Gwilym M.: Vaginal Metastases From Carcinoma of the Ovary, J. Obst. & Gynaec. Brit. Emp. 59: 82, 1952.**

This case report of vaginal metastases from carcinoma of the ovary is of unusual interest because of the extreme rarity of metastases to the vagina from such malignancy. Only 3 cases have been recorded in the literature and many standard textbooks on gynecology and gynecological pathology do not mention the lesion. The case in point was that of a 65-year-old spinster whose last menstrual period occurred at the age of 49 years and who had had no vaginal bleeding until the present time 14 years later. On laparotomy bilateral malignant ovarian cysts were removed, followed by total hysterectomy. There were found secondary implantations in the vagina. Microscopic sections of the ovarian and vaginal lesions showed adenocarcinoma very similar in histological appearance. The origin and relationship of ovarian and vaginal malignancy are considered and the literature reviewed. The author concludes "that ovarian tumors represent the primary growth and that the vaginal tumor is a secondary carcinoma, which has arisen as the result of retrograde lymphatic embolism."

HARVEY B. MATTHEWS.

### Endocrinology

**Caldwell, Bettye McDonald, and Watson, Robert I.: An Evaluation of Psychologic Effects of Sex Hormone Administration in Aged Women, J. Gerontol. 7: 228, 1952.**

Psychic rejuvenation of the aged woman has been attempted by the administration of estrogen and progesterone cyclically for relatively long periods of time. Thirty aged women whose mean age was 75 years were selected for a study designed to investigate the psychologic effects of the female sex hormone. Half of the patients received injections of estrogen and progesterone in a dose sufficient to induce cyclic bleeding while the other half received injections of a neutral oil. The patients who received the estrogen and progesterone were first primed by the administration of estradiol in a dose of 3 mg. per week over a period of six weeks. Then estrogen was administered cyclically together with progesterone to induce the bleeding.

Prior to the introduction of hormone therapy and again six months after therapy a battery of psychologic tests were administered. The tests were chosen to evaluate such human functions as general intelligence, memory, energy level, initiative, and thought processes. The results of this analysis showed many favorable trends which may be attributed to the estrogen-progesterone administration. Intellectual functioning, although not uniformly at a higher level, showed improvement, in so far as ability to think and willingness to extend intellectual energy were concerned. Memory was enhanced and gains in the ability to learn new material were observed. A reawakening and reorientation of the aged female toward a fuller intellectual life were seen during and following the administration of estrogen and progesterone.

WILLIAM BICKERS.

### Gynecology

**Deacon, A. L., and Taylor, C. W.: Hydradenoma of the Vulva, J. Obst. & Gynaec. Brit. Emp. 59: 64, 1952.**

In 1904 Pick described certain tumors of the vulva of sweat-gland origin which he called hydradenomas. During a ten-year period (1940 to 1950) 90 simple cysts and neoplasms of the vulva, excluding those of Bartholin's gland and endometriosis, were examined pathologically at the Birmingham and Midland Hospital for Women, 12 (13.3 per cent) of which were diagnosed as hydradenomas. Simple excision was carried out in each of these cases. The origin of these tumors must be discussed with full knowledge of the different types of skin glands. These are (1) the holocrine group; (2) the merocrine group; and (3) the apocrine group. It is from the latter group that the hydradenomas most often arise, though rarely origin may be from merocrine glands. Hydradenomas are most commonly found on the labia majora but may occur on all other areas of the vulva, except the labia minora which are usually devoid of apocrine glands. They are most common between the ages of 30 and 50 years, although the authors had a case at age 19. A very detailed macroscopic and microscopic description of these 12 tumors is given along with 7 photomicrographs depicting the histopathology of the various types of hydradenomas. The question of malignancy is discussed and the conclusion drawn that such tumors are very rarely malignant, although 3 cases in this series were suspicious and required meticulous study to rule out malignancy. Other writers report that malignancy quite frequently occurs, one in 27 per cent of cases; another makes the claim that all hydradenomas are of low-grade malignancy. The authors do not state whether or not their cases were followed up for 5 years which, of course, is required before malignancy can be ruled out clinically.

HARVEY B. MATTHEWS.

**Asplund, Jan, and Rydén, Ake B. V.: The Diagnosis of Tuberculosis of the Cervix, Acta obst. & gynec. Scandinav. 32: 186, 1952.**

The authors studied 19 patients with coexisting tuberculous salpingitis and endometritis, and found tuberculous cervicitis to be present in 11 of these women. There were no specific symptoms referable to the lesions. Four chief histologic and gross pathologic types of the lesion are described: papillary, ulcerative, interstitial, and endocervical. Hysterosalpingograms were done on all the patients in this series, but in no case was there any definite roentgenological indication that the cervix was involved. The authors believe that the only accurate method of diagnosis is by curettage, and they suggest that this be done fractionally, i.e., without dilatation of the cervical canal, since this procedure disturbs the morphologic features of the lesion to some extent. Curettage should be undertaken in any patient who has proved tuberculous endometritis or salpingitis.

DOUGLAS M. HAYNES.

**Falconer, B.: Investigations Into the Uterine Mucosa. VIII. A Comparative Study of the Functional Activity of the Endometrial Glands and the Endometrial Stroma, Acta obst. & gynec. Scandinav. 32: 162, 1952.**

Falconer here presents another contribution in his exhaustive series of investigations into various aspects of the histology of the endometrium. Evidence is adduced to support the idea that microscopic appearances of both the stroma and the glands should be carefully studied when attempting to assess the status of a given endometrium. It is probable that the endometrium does not attain the acme of its development in every menstrual cycle, so that various confusing mixtures of histologic features may be noted in any given case. His studies lead Falconer to the conclusion that the specific function of the endometrial glands in the normal cycle is less important as regards the potentially nidating ovum than is the specific function of the stroma. The latter appears to be more susceptible to injury than the epithelium, so that disturbances of endometrial growth are possibly more sensitively mirrored in the histological appearance of the stroma than in that of the glands. He suggests



that the diagnosis of phase, whether proliferative or secretory, ought not to be made with positivity unless it has been verified that the stage of development of the stroma corresponds to that of the epithelium. Thus, microscopic findings of secretory glands alone do not justify the diagnosis of secretory phase.

DOUGLAS M. HAYNES.

### Gynecologic Operations

**Kühnel, Poul:** Experience With Le Fort-Neugebauer's Operation for Complete Prolapse, *Acta obst. & gynec. Scandinav.* 31: 151, 1952.

The results obtained in 58 cases of complete genital prolapse treated by the operation of partial colpectomy (Le Fort-Neugebauer operation) are reported. The operation was combined with perineorrhaphy in 77.6 per cent of the patients. Eighty-three per cent of the procedures were carried out under local anesthesia. The patients' ages ranged from 47 to 77 years. Two patients died, constituting a mortality rate of 3.5 per cent. The results were considered satisfactory in 99 per cent of the survivors; either there was complete relief of symptoms, or very material improvement over the original situation was noted. There was recurrence of the prolapse postoperatively in three patients, and this followed postoperative hemorrhage necessitating insertion of vaginal packs in two of these. The author believes that this operation is indicated in many cases of complete genital prolapse in the postmenopausal age group in whom the risk of operation is considerable. One-half of the author's patients suffered from degenerative cardiovascular disease. The procedure is not recommended for incomplete prolapse: in this situation, the author prefers the Manchester-Fothergill operation.

DOUGLAS M. HAYNES.

### Menstruation, Dysmenorrhea

**Kneer, M.:** Treatment of Functional Amenorrhea and Metrorrhagia, *Deutsche med. Wchnschr.* p. 141, Feb. 1, 1952.

Of the many disturbances of the menstrual cycle, the absence of the menses or increased abnormal amounts of menstrual bleeding are of paramount interest. The author, having eliminated all pathological entities, presents a discussion of the functional changes which occur in the ovary, the pituitary, or the neuroendocrine system resulting in amenorrhea or metrorrhagia. The paper, therefore, deals with the diagnosis and endocrine therapy of such disturbances. The basic viewpoint is that many abnormalities of the menstrual cycle are symptoms of internal derangements which can be diagnosed by complete history, minute physical examination, and extensive laboratory procedures. Three main classes of amenorrhea are listed:

1. The so-called exogenous group, which includes all cases not primarily connected with ovarian function. Among these are malnutrition, climatic changes, extreme psychic or emotional shock, and metabolic disturbances. The history gives the main lead, since all laboratory and physical tests are negative. All therapy, other than correction of hypothyroidism, hypoproteinemia, hypovitaminosis, or anemia, is considered unnecessary for these cases.

2. The second group includes those cases in which the central regulating mechanism of ovarian function is disturbed, which mechanism is probably located in the diencephalon or in the midbrain. Thus basic causes may be severe psychic trauma; toxemia of severe infection; encephalitis; severe hemorrhage or other conditions affecting the central nervous system. In this group the menstrual dysfunction is merely one of a number of symptoms and treatment should be directed against the primary cause wherever possible.

The third group includes those cases directly due to ovarian deficiency. These are relatively few in number, and include at most only 20 per cent of all cases of amenorrhea.

Diagnosis must be accurately made before therapy can be started. The biological or chemical assay of hormones is difficult and impractical. Procedures found to be helpful in

diagnosis included: (1) curettage or endometrial biopsy; (2) cytological studies of exfoliated vaginal cells; and (3) basal temperature charts. With these, the absence of ovarian function, changes in ovarian function, and levels of the ovarian hormones could be determined with sufficient accuracy if the procedures were followed for a minimum of three calendar months. Where ovarian dysfunction had been diagnosed, 48 per cent of the cases showed complete afunction of the ovaries; 17 per cent showed deficient follicle hormone production; 21 per cent showed hyperovarianism; and the remainder normal ovarian hormones.

In all cases, treatment included a high-protein, high-vitamin diet, together with rest, easier work, and better working conditions. These general procedures gave better results than specific endocrine therapy. Thyroid was also given when the basal metabolism was low. Therapy was most unsuccessful when pituitary deficiency was diagnosed. The use of diathermy, vitamin E, x-ray stimulation, and other physical methods was unsuccessful. Anteron and other supplemental pituitary hormones were without value. Best results were with intramuscular injections of a saline solution of macerated calf pituitary. In ovarian hypofunction, estrogens and progesterone caused bleeding, which bleeding was due to the administration of the hormones and not to improved function of the gland. However, it was felt that if this cyclic bleeding could be maintained for months, the probability of continued menstruation was good. If no results were obtained with this therapy the author recommended the continuation of such treatment for three months before abandonment.

Functional metrorrhagia was found to be due to insufficient production or absence of corpus luteum hormone, or to excessive estrogen formation (cystic glandular hyperplasia). This, the author felt, was probably due to basic pituitary changes. Diagnosis is suggested by history and physical examination. On pelvic examination, definite changes in the portio vaginalis, increase in the size of the uterus, together with the presence of enlargement of the ovaries, are indicative of this condition. Diagnosis is proved by histological examination of endometrial tissue. In treatment, x-ray and radium are not recommended even in the menopause because of the possibility of carcinoma and because of the development of still greater bleeding at a later date. The best results were obtained by continued hormonal therapy, utilizing either (1) chorionic or equine gonadotropin, (2) progesterone, or (3) testosterone. With the latter two, severe bleeding could be controlled in a very short time when the hormones were given in large doses. Progesterone was given by intramuscular injection in doses of 100 mg. which always controlled the blood flow. In order to maintain the improved status, progesterone, as crystalloid Proluton, was given in maintenance doses together with small doses (5 to 10 mg.) of estrogens. Testosterone was administered in doses of 50 mg. It was often found necessary to give 4 to 6 injections over a short period before bleeding was controlled. Eighty per cent of all cases thus treated showed good results. Therapy with either drug had to be continued over several months.

L. B. WINKELSTEIN, M.D.

**Salvatore, Carlos Alberto: Capillary Fragility and Menstruation, Surg., Gynec. & Obst. 95: June, 1952.**

The author studied capillary fragility in 60 women ranging from the age of 16 to 44 years who had normal menstrual cycles and normal arterial pressure. Utilizing a medium pressure for 3 minutes and looking for petechiae on the forearm under the blood pressure band, he considered as normal the presence of no more than 9 petechiae in women who were not menstruating. During the first days of the menstrual period there was a slight increase in the capillary fragility and up to 15 petechiae appeared. This seems to bear out the work of Brewer and Tey who also demonstrated an increase in capillary fragility during the first days of menstruation.

The author feels that this increase in fragility is due to a deprivation of estrogen.

L. M. HELLMAN.

### Miscellaneous

**Nicholson, D. B., and Assali, N. S.: Hematologic Response of the Pregnant Woman to Intravenous Saccharated Iron Oxide, Surg., Gynec. & Obst. 94: 513, 1952.**

The authors report a very small number of patients treated with intravenous saccharated iron, given in 200 mg. doses, approximately 3 times a week. The response was measured by determining the hemoglobin, erythrocyte count, and reticulocyte count before and after the injection. There were 4 control patients, 6 prepartum anemic patients (hemoglobin between 8 and 10 Gm.) and 6 anemic postpartum patients. Saccharated iron oxide therapy promotes immediate erythropoiesis in patients with microcytic anemia in pregnancy, the degree of response being in general directly proportionate to the severity of the anemia. Relatively large amounts of iron may be given in a short period of time. The hematologic response is initially more rapid than that obtained with oral iron.

L. M. HELLMAN.

**Held, H. R.: The Passage of Fluorides Through the Placenta and Excretion of Fluorides in the Milk, Schweiz. med. Wchnschr. 82: 297, 1952.**

The question as to whether salts of fluorine are able to pass through the placental barrier during pregnancy, as well as whether they are excreted in human milk, has never been accurately determined. This utilization of fluorides may have great importance in the development of healthy teeth as well as the prevention of caries in the deciduous teeth of the child. Many authors, including the American workers, believe that ingestion of fluorides by the mother during pregnancy has no effect on the unborn child, since it is only very slightly available to the fetus. They also feel that very little or no fluoride is excreted in the milk. On the other hand, Swiss and other European researchers feel that the use of fluorides during pregnancy and lactation is beneficial, in that the incidence of caries in the child is less in treated than in untreated mothers. Furthermore, in human beings, no chemical study or evidence is available to show passage of fluorides through the placenta or into the milk. In order to clarify the situation and if possible reconcile the opinions of many workers, the author attempted to determine accurately in pregnant, parturient, postpartum, and nursing women definite quantitative chemical studies of fluorides in the maternal blood, the placental blood, the cord blood, the milk, and the urine.

Investigation of fluoride transfer through the placenta was made during pregnancy, during labor, and immediately post partum. Blood samples of maternal venous blood and blood from the cord and from the placenta were assayed for fluorine content and comparisons made. In those cases where the maternal fluorides were relatively low (172 to 250  $\gamma$  per cent), the fetal fluorides were always higher than the mother's (244 to 250  $\gamma$ ), but where the maternal fluorides were high (250 to 389  $\gamma$ ) the fetal levels were lower (250 to 316  $\gamma$  per cent). Similar findings were noted in premature deliveries and in multiple births. Conclusions were therefore reached that (1) fluorides are actively passed by the placenta; (2) high blood concentrations in the mother mean high blood levels in the baby, but not in direct proportion; and (3) that the placenta does not store or withhold fluorides.

In an attempt to raise the fluoride level of the mother, 5.0 mg. of sodium fluoride was given twice daily for a period of five days. In all cases the maternal blood level increased from 14 per cent to 92 per cent, which the author feels was probably reflected by increased fluoride content of the blood of the child.

A study of the relationship of the fluoride content of the blood of nursing mothers and of the fluoride content of the milk was also made. It was found that the amount of fluoride present in the milk was approximately one-third of the level found in the blood. This was found to be rather constant and was not influenced in any way by either the maternal level or the ingestion of fluorides. In a controlled series of cases where the mother was given 10 mg. of sodium fluoride per day for five days the maternal level increased but the amount present in the milk remained approximately the same.

L. B. WINKELSTEIN.

### Newborn

**Gross, Robert E., and Ferguson, Colin C.: Surgery in Premature Babies. Observations From 159 Cases, Surg., Gynec. & Obst. 95: 631, 1952.**

Infants and small children cannot be treated surgically as diminutive adults but must be handled with great care and with specially designed operative techniques. The premature infant demands even more delicate supervision and consideration. Report is made of 212 operations over a period of 16 years on 159 premature infants who weighed 5 pounds or less, average weight 4 pounds, 3 ounces. The smallest to survive weighed 2 pounds, 6 ounces. Eighty-seven (54 per cent) of the 159 survived. This survival rate was increased among 19 premature infants operated upon in 1951, when 15 (79 per cent) survived.

Neonatal physiology is reviewed with special emphasis on the inadequacies and limitations peculiar to the premature infant:

**Bodily temperature and metabolism:** The premature infant is extremely susceptible to variations in environmental temperatures.

**Respiratory system:** The respiratory movements of the newborn are almost entirely diaphragmatic.

**Cardiovascular system:** The premature infant is particularly susceptible to alterations in blood volume such as occur in shock, blood loss, or overhydration. The plasma protein levels are universally low. The resulting diminution in plasma osmotic pressure, in combination with increased permeability of the capillary bed, facilitates the formation of edema. A hemorrhagic tendency may develop by the third day of life.

**Alimentary system:** The bowel is especially prone to distention.

**Urinary system:** Physiologic immaturity is shown by the limited process of urinary concentration, low clearance levels of urea, sodium, and chloride, and by frequent albuminuria.

The principles of surgical care are discussed in considerable detail, such as warm constant temperature, environment, attention to respiratory system, and isolation.

Preoperatively, vitamin K, penicillin, and atropine are administered but no sedative. A needle is inserted into the antecubital or median ankle vein. Local anesthesia is safest but by no means the most satisfactory. Cyclopropane is the agent of choice. The shorter the length of time the premature infant is subjected to anesthesia and operative trauma, the better are his chances of survival.

For the premature baby it is more rewarding to rely on "clinical" judgment; only rarely need laboratory aids be employed, postoperatively.

The amount of parenteral fluids is preset. For four or five days after surgery a baby that is taking nothing by mouth should not be given more than 30 c.c. per pound per 24 hours, divided into two or three administrations. The authors have seen many infants die because of excessive administration of parenteral fluid and do not recall one that died of dehydration. Intravenous blood, plasma, or albumin is frequently necessary but saline solution should be avoided.

When gastric decompression is necessary it should be accomplished through a No. 18 or 10 French urethral catheter intermittently. Feeding should be by gavage.

Postoperatively phenobarbital (2 to 6 mg.) may be given every 6 to 8 hours. Constant nursing care is essential to detect complications which are predominantly respiratory in nature. Antibiotics are almost routine postoperatively and thrush is frequently encountered following their administration. When it occurs, antibiotics should be discontinued and sulfonamides substituted if indicated.

A list of the 87 cases of infants who survived is presented together with diagnosis, weight, and operative procedure.

L. M. RANDALL

**Müller, H. K.: Concerning Embryopathia Rubeolosa, Med. Klin. 18: 611, 1952.**

The deleterious effect of rubeola (German measles) on the early development of the fetus has been known for a long time. The literature contains many case histories of



microcephalus, cataracts, cardiac anomalies, and other pathological entities occurring in the baby because of maternal infection during the first trimester of pregnancy. Since the virus of rubeola is easily able to traverse the placenta, it can affect the embryo at any stage of gestation. This effect, however, results in the greatest damage in the stage of actual development rather than in the growth stages. The author feels that similar malformations may occur, not only with German measles, but also with other virus diseases, especially measles, mumps, chicken pox, and poliomyelitis. No known prophylactic measures are available since these virus diseases cannot be spread before pregnancy occurs, and thus produce immunity. Likewise, no known therapeutic agent is available for curative purposes once the disease does develop.

The author feels, however, that, while a causal relationship does exist, the effects are very much overrated, since many similar fetal anomalies have been found where none of the virus infections have occurred during pregnancy. He feels therefore that while embryopathia rubeolosa can adversely affect the baby, it is not, nor should it be, an indication for interruption of the pregnancy.

L. B. WINKELSTEIN

**MacCarthy, D., Douglas, J. W. B., and Mogford, C.: Circumcision in a National Sample of 4-Year-Old Children, Brit. M. J. 2: 755, 1952.**

The incidence of circumcision in 2,428 4-year-old British boys who had been born in March, 1946, was 24 per cent. More than one-third of these circumcisions were done during the first month of life when faults or diseases of the prepuce itself are practically nonexistent, since the two inner surfaces of the prepuce may not separate to form a preputial space until after the age of 3 years. The higher the economic status of the family, the greater the incidence of circumcision. Five per cent of the circumcised children had complications such as second operation, hemorrhage, or sepsis of the penis.

WILLIAM F. FINN

**Dippel, A. Louis: The Prevention of Erythroblastosis Fetalis by the Use of Rh Hapten, South. M. J. 45: 954, 1952.**

Since the discovery of the Rh factor and its implication in the production of erythroblastosis fetalis an effort has been made to find some neutralizing substance for the Rh antigen.

In an attempt to neutralize the Rh antibodies in the sensitized mother various drugs and compounds have been tried. Rh hapten is prepared as an extract from outdated Rh-positive blood taken from the blood banks of hospitals. The product is a cholesterol-like lipid with few or no antigenic properties. Several cases are reported in some detail, in some of which it would appear that the Rh hapten therapy had been productive of a nonerythroblastotic child where without therapy one would have been expected. One case in particular resulted in a normal child from a woman who had been isoimmunized from transfusion and it is well known that transfusion isoimmunization is more lethal obstetrically and responds much less readily to therapy than sensitivity induced by Rh-positive offspring. This patient had delivered one severely damaged erythroblastotic fetus and after a treated pregnancy delivered a normal child.

Many points need clarification. Size of dose and frequency of administration for different types of cases must yet be worked out. The authors do not claim any great universal application for the Rh hapten but do think it is worthy of further investigation.

WILLIAM BICKERS

**MacCarthy, D., Walker, A. B. C., and Matthews, S.: Scalp Abscess in the Newborn; a Discussion of Their Causation, J. Obst. & Gynaec. Brit. Emp. 59: 37, 1952.**

In 19 newborn infants at the Postgraduate Medical School of London, there was a scalp lesion in the right parietal region; in 9 of these cases the lesion was an abscess and in 2 there was a sequestrum from the parietal bone. Delivery was by forceps in 15 cases and spontaneous in 4 cases; in most cases labor was prolonged. In the forceps deliveries there

were 2 cases in which there was also a lesion on the left parietal region, but the lesion on the right side was more severe. In forceps deliveries, such lesions in the right parietal region are attributed to injury by the right forceps blade. In spontaneous deliveries in which labor is prolonged, there may be prolonged pressure on the right parietal bone, which causes ischemic necrosis and predisposes to infection. In an ordinary lying-in ward, strict aseptic technique cannot always be maintained, and staphylococcus infection is of frequent occurrence. Hence it is important to examine the infant's scalp carefully after forceps delivery, and any abrasion found should be given local treatment and appropriate antibiotic treatment should be begun at once. Delay in labor, especially in the second stage, should be avoided; if forceps are to be used the head should be fully rotated manually before the forceps are applied, to prevent further injury to the right parietal region of the infant, which may have been submitted to considerable pressure during the process of labor before the forceps are used. Willett's forceps should not be used in cesarean section for delivery of the head, as this may also cause an injury to the infant's scalp, which as in other similar injuries may become infected, with resulting abscess formation.

HARVEY B. MATTHEWS

**Davidson, Harold:** Penicillin in the Prophylaxis of Ophthalmia Neonatorum, Obst. & Gynec. Surv. 7: 147, 1952.

This article is a complete review of the treatment of ophthalmia neonatorum from the time of the first publication of Clay Day over 70 years ago. It not only covers the use of silver nitrate but also is a complete report of the experimental use of penicillin in the treatment of gonococcal ophthalmia. The author quotes extensively from his own findings in which 9,241 consecutive newborn infants were treated with penicillin intramuscularly without a single case of gonorrheal ophthalmia. In a further, and well-controlled experiment, the author used both penicillin ointment and silver nitrate in the eyes in a weekly rotation. A table is shown indicating the incidence of local irritation. When the penicillin ointment was used this incidence was 10.6 per cent; when intramuscular penicillin was used the incidence was 13.8 per cent, but with silver nitrate the incidence of irritation rose to 51.3 per cent. The authors are of the opinion that penicillin ointment is by far the best prophylactic agent for gonorrheal ophthalmia and in those communities where statutes or board of health regulations allow only silver nitrate it is recommended that these regulations be changed.

L. M. HELLMAN

### Pregnancy, Complications

**Logan, W. P. D.:** Incidence of Congenital Malformations and Their Relation to Virus Infections During Pregnancy, Brit. M. J. 2: 641, 1951.

The author states the purpose of his study to be a review of the known incidence of congenital malformations and to summarize what is known concerning the effect of virus infections during pregnancy. In the three-year period (1946-1948) congenital malformations caused 12 per cent of the infant deaths and ranked third in the causes of infant death, preceded by prematurity and pneumonia. The infant mortality rate from congenital malformations was computed to be 6 per 1,000 live births in the period 1931-1939, with an increase to 6.5 per 1,000 in the period 1940-1952, and a subsequent decline in 1948 to 4.45 per 1,000. Total infant mortality declined proportionally in the same period. Since there was no reason to believe that the incidence of congenital malformations declined, the author presumes that the reduction in mortality is related to the preservation of life in infancy in such cases. The author reviewed various series in the literature and found that the average incidence is 2.23 per cent. He points out that Murphy of Philadelphia gave an erroneous impression of actual incidence (1 in 213 live births) since he analyzed only death certificates. Most series report incidences closely approximating 1 in 40. The author summarized the work of Swan and Gregg concerning the effect of maternal rubella in pregnancy. He emphasized the fact that these studies were *retrospective* and are consequently

misleading because the cases of malformation were selected before inquiry about the pregnancy was made: and, second, the mother's recollection may have been faulty or influenced by the fact that she had delivered a malformed child. He suggests, therefore, that the actual risk has been greatly exaggerated and doubts the statistical evidence which has led to the acceptance in some circles of the policy of early therapeutic termination of pregnancy in cases of known rubella in pregnancy. A review of the literature from a *prospective* point of view, giving an analysis of results in patients known to have had various virus diseases in pregnancy, is included in the article. The author states that the results are confusing and inconclusive. Finally, he states what are in his opinion the desirable features of any prospective study whose object is to determine the effect of maternal rubella or other virus diseases on the development of the fetus.

DONALD G. JOHNSON

**Johnson, Lloyd W., and Moir, J. Chassar: A Case of Angular Pregnancy Complicated by Gas-Gangrene Infection of the Uterus, J. Obst. & Gynaec. Brit. Emp. 59: 85, 1952.**

This is a report of a case of angular pregnancy complicated by gas-gangrene infection of the uterus. A woman, aged 31 years, para ii, 16 weeks pregnant, was admitted to the Kingston General Hospital with severe lower abdominal pain and vaginal bleeding. She admitted attempted self-induced abortion. A diagnosis of infected abortion was made and appropriate treatment instituted. Ten hours after admission she suddenly went into shock from evident intraperitoneal hemorrhage. After blood transfusions and other supportive treatment were given, laparotomy was performed and about 3 L. of blood removed. Supracervical hysterectomy was rapidly performed. Drainage was accomplished through the cul-de-sac through the vagina. Rupture of the uterus in the region of the right cornu had taken place. Gas bubbles were seen coming from the rent in the uterus. The patient died 8 hours after operation in spite of vigorous treatment. At autopsy the most remarkable features were the intense jaundice; hemoperitoneum; submucosal hemorrhages; extravasation of blood in abdominal and pelvic sites of operation. The kidneys were severely damaged showing extensive interstitial hemorrhage and necrosis. Bacterial stains revealed *B. Welchii* in massive quantities. This case is illustrative of what the author describes as an angular pregnancy but which undoubtedly had extended into the interstitial portion of the uterine wall. Such a pregnancy, if rupture occurs, ruptures into the peritoneal cavity whereas an angular pregnancy extrudes itself into the uterine cavity.

HARVEY B. MATTHEWS

**Reeves, David L.: Tumors of the Brain Complicating Pregnancy, West. J. Surg. 60: 211, 1952.**

Tumors of the brain complicating pregnancy represent an infrequent neurosurgical and obstetrical experience. Six cases are here presented, each one different from the others and presenting separate and distinct problems. It becomes apparent that each case should be studied individually and treated according to its own peculiarities.

Evidence of increasing intracranial pressure, as manifested by visual disturbances, Jacksonian type convulsions, severe and progressive headache, vomiting, and other central nervous system signs, calls for early intervention. Cesarean section is the safer procedure under such circumstances. Electroencephalographic tracings taken during pregnancy may indicate those with intracranial expanding lesions and lead to appropriate consultations and additional diagnostic procedures. While any surgical intervention in the pregnant woman increases her chances of abortion, the prolongation of life which follows removal of a glioma or astrocytoma increases the survival chances of the fetus.

Pregnancy exaggerates the symptoms of an expanding intracranial lesion because it favors edema. The changes in water metabolism and the tendency toward water storage in pregnancy increase the tissue edema about the tumor site and often precipitate symptoms of the tumor earlier than would otherwise be the case.

WILLIAM BICKERS



**Gantsbauer, H.: The Relation of Dental Foci of Infection to Obstetric and Gynecologic Complications, Deutsche med. Wchnschr. 77: 738, 1952.**

The importance of focal infections of the teeth has been known for a long time, but, in general, has been either completely disregarded or greatly underestimated. Furthermore, although resultant infection elsewhere in the body is easily recognized, the relationship between the new infection and the old focus in the mouth has not been usually correlated. Little attention has been given to this factor either in the history or in the examination of obstetrical and gynecological patients. The author has recognized this omission in the medical care of patients and has cautioned against this minimization of dental infection and dental caries. In a great many instances he has been able to demonstrate a direct relationship between these focal infections in the teeth and mouth with both generalized and local infections throughout the body. Hence, he cautions that in all surgical cases which are not of an emergency nature the teeth should be inspected, examined, and treated before definitive pelvic therapy is undertaken. Complete dental check-ups, including dental x-rays, should be completed in every gravid woman early in pregnancy. All caries, infections, extractions, and other dental procedures and surgery should be attended to before the fifth month of gestation. The observation is further made that dental focal infections may be the direct cause of many cases of acute or chronic mastitis, thrombophlebitis, puerperal sepsis, and vaginal and pelvic abscesses of unknown origin.

L. B. WINKELSTEIN

**Donaldson, Ian A.: Pelvic Tuberculosis and Pregnancy, Brit. M. J. 2: 128, 1952.**

Two cases of intrauterine pregnancy associated with pelvic tuberculosis are reported. The author fails to state whether or not tuberculosis was demonstrated in the endometrium either histologically or by culture. The first case, terminating in an abortion, was not documented histologically as to the pelvic organs, even though three operations had been performed. The omentum only was studied histologically after two operations, and it was positive for tubercles at the second operation. A biopsy of the left shoulder capsule was positive for tubercles. No such proof is presented of the presence of tubercles in the pelvic organs or in the curettage specimen obtained after the abortion. Tubal tuberculosis was discovered, at laparotomy, in the second case six months after delivery of a full-term infant. The tubes were studied histologically, but not the endometrium.

The author presents a fairly complete review of the literature and emphasizes the rarity of pelvic tuberculosis and pregnancy.

The references are made to cases of extrauterine and intrauterine gestation, spontaneous abortion, and delivery of viable children.

CARL T. JAVERT

**Alimurung, Mariano M., and Manahan, Constantino P.: Typhoid in Pregnancy: Report of a Case Treated With Chloramphenicol and ACTH, J. Philippine M. A. 28: 388, 1952.**

The authors of this paper report the first case of typhoid fever in the Philippines treated with Chloramphenicol (chloromycetin) in conjunction with ACTH. The case happened to be complicated by a five months' gestation.

There was a dramatic clinical response in this patient twenty hours after the ACTH was begun even though the dose given (100 mg. over a four-day period) was less than recommended by previous observers in the United States.

When it is realized that pregnancy complicated by typhoid fever results in miscarriage or premature labor in 60 to 80 per cent of cases, a fetal mortality of 75 per cent, and a maternal mortality of 15 per cent, it is significant that this patient who was severely ill recovered and went to term, delivering a healthy 8 pound, 4 ounce infant.

EUGENE N. SCADRON

**da Costa Barros, Albertino: Obstetrical Hemorrhages, Rev. port. obst. ginec. e cir. 4: 5, 1951.**

The author in this extensive paper reviews and discusses the field of obstetrical hemorrhage in great detail, touching on etiology, anatomic pathology, morbid anatomy,



treatment, and prognosis. Tubal abortion, tubal pregnancy both ruptured and unruptured, early uterine abortion and miscarriage, placenta previa and premature separation of the placenta, and postpartum hemorrhage. Hydatidiform mole and choriocarcinoma are all discussed in general, and in particular the cases in the author's series. This is truly a complete thesis on the subject of obstetrical hemorrhage, the principal cause of maternal mortality.

RICARDO L. GORBEA

### Puerperium

**Wallis, Henry:** *Resuturing of Broken-down Episiotomies*, Rev. obst. y ginec., Caracas 12: 216, 1952.

The author in this paper presents an analysis of the results obtained in 80 cases of infected and dehiscenced episiotomies, treated by resuturing.

The surgical preparation, technique used, and postoperative care are explained in detail. The end results were tabulated as follows: (1) complete closure by primary intention, 81.2 per cent; (2) closure by secondary intention, 11.2 per cent; and (3) failures, 7.5 per cent. The resuturing of dehiscenced and infected episiotomies is strongly recommended by the author.

RICARDO L. GORBEA

### Radiation

**Rubin, I. C.:** *Third Generation Follow-up in Women Receiving Pelvic Irradiation*, J. A. M. A. 150: 207, 1952.

The author reports his results and experiences with the use of low-dosage x-ray radiation to the ovaries and pituitary with reference to human reproduction. Comparisons are made between the radiation of the fruit fly and that of the human ovary. There are certain incomparable biologic and constitutional differences between the fruit fly and the human species. The immediate irradiation effect on human ovaries is essentially dissimilar to that in the fruit fly because of the anatomic structure and position of the ovaries in relation to the overlying tissues. The dose to each human ovary as applied in the treatment of recurrent amenorrhea and infertility is about 175 r. According to D. F. Lea, the 50 per cent dose for a batch of *Drosophila* eggs irradiated within 30 minutes of laying when usually not more than one or two nuclear divisions have occurred is 290 r. Young women can recover ovarian function, become pregnant, and give birth to normal children after receiving a castration dose of x-ray. The author reports a case in which a normal full-term male child was delivered the father of whom had been born of a mother who had x-ray stimulation for sterility. According to the author no acquired lethal effects on the genes have been observed in hundreds of babies born following x-ray treatment for the relief of infertility.

WM. BERMAN

**Vara, Paavo, and Halminen, Eero:** *On Fetal Electrocardiography*, Acta obst. & gynec. Scand. 32: 179, 1952.

Fetal electrocardiography was performed on 92 patients studied at the Second Women's Clinic of the University of Helsinki. Suprasymphyseal and fundal leads were used, while in very early pregnancy a specially refined electrode composed of a silver cup attached to an insulated stem was added. The recordings were made by an oscillograph furnished with a camera, and the impulses were amplified by means of a powerful differential amplifier. The earliest month in which successful recordings were obtained was the third, so that this method is not a diagnostic competitor with the various biologic tests for pregnancy. Fetal electrocardiography is, however, incapable of giving a "false positive" result, so that it might occasionally be useful in determining whether or not the fetus is alive in cases where

fetal life cannot be confirmed by other means. Theoretically, this method should permit earlier diagnosis of multiple pregnancy than is available by other methods, but the authors had no illustrative case to bear this out.

DOUGLAS M. HAYNES

**Nolen, James F., and Du Sault, Lucille:** The Elimination of Untoward Radiation Sequelae in the Treatment of Carcinoma of the Uterine Cervix, Surg., Gynec. & Obst. 94: 539, 1952.

In a statistical analysis of 214 patients with carcinoma of the cervix in clinical Stages I, II, and III, the authors have attempted to study the clinical occurrence of factitial radiation reactions. The complications which were known to depend upon the amount of radiation delivered were selected and their incidence compared to the incidence of successful treatment which depended upon the stage of the disease and the dose delivered. The question asked was whether the complications studied should be accepted as a necessary sequel to successful treatment.

The findings seemed to suggest that in mild cases (Stage I), such complications were not necessary if cure was to be effected. However, in Stage II carcinoma, cure was necessarily accompanied by a definite percentage of gastrointestinal and urinary tract complications.

L. M. HELLMAN

### Sterility

**Asherman, J. G.:** X-ray Therapy of Sterility, Gynaecologia 133: 65, 1952.

Soon after the stimulating effect of roentgen rays was discovered, European workers, treating functional disorders of menstruation by irradiation of the ovaries, repeatedly met with pregnancies, in many cases where any possibility of pregnancy seemed out of the question. Nevertheless, they refused to recommend, for many reasons, the use of x-ray therapy for the treatment of sterility. American authors, however, were more daring, and advised the use of roentgen therapy not only to the ovaries, but also to the pituitary, for both the treatment of functional amenorrheas and also for sterility. Many hundreds of successful results were thus obtained. However, despite a great deal of experimental research, the value of pituitary irradiation is still under dispute. It is well known that the pituitary is very radioresistant, and yet results were obtained in cases where pituitary irradiation alone was employed. The author has attempted to clarify this situation by the treatment of 90 cases of sterility by the use of combined ovarian-pituitary irradiation as compared to irradiation of the pituitary alone. All cases were studied in Israel during the years 1947 and 1948, and were of the type where all other kinds of therapy to combat the sterility had failed.

In a general study of all cases treated, it was found that an immediate and complete regulation of the menstrual cycle with biphasic temperature graphs was observed in 36 per cent. Twenty-five patients conceived within the first 6 months, 5 more within a year, and 4 more during the second year. Twenty-nine cases did not respond to therapy at all. Moreover, it was noted that 13 per cent of all cases, regardless of which type of therapy was used, lost their menses entirely and entered an artificial permanent menopause. Although over half of these women were more than 35 years of age, it was felt that radiation therapy is not a procedure which can be indiscriminately recommended since it does bear the possibility of the production of unfavorable and embarrassing results.

The 90 cases studied were divided into groups according to the type of pathology noted. Irradiation in normal cases, i.e., where history, physical examination, and basal temperature charts were within normal range, was unproductive of pregnancy in any instance. Similar results were obtained where congenital anomalies were noted to be present. Irradiation in cases where anovulatory cycles were observed or where the menses occurred at grossly irregular long intervals produced the best results, in that over 40 per cent of these patients became pregnant, carried to term, and were delivered of normal offspring.

The value of combined irradiation to the pituitary and ovary, as compared to irradiation of the ovary alone, is expressed briefly in the following; (1) If considering the regulation of the menses alone, 43 per cent were improved with the combined therapy as compared with 28 per cent improved with only pituitary irradiation. (2) When resulting pregnancies are the deciding factor, 43 per cent became pregnant with combined ovariopituitary therapy as compared with 23 per cent when the pituitary alone received stimulation. (3) On the negative side, only 21 per cent had no effect whatsoever with the combined irradiation, as compared with 44 per cent when only the pituitary was stimulated. The conclusions reached, therefore, are that the pituitary is not completely radioresistant, and that irradiation of that organ does produce a noticeable effect on the ovaries; that irradiation of both organs is approximately twice as effective as pituitary stimulation alone, and that the beneficial effect is due to the re-establishment of normal ovulation and ovarian function both by stimulation of the ovary directly and by increased hormone stimulation from the anterior pituitary. It was to be noted, moreover, that all offspring thus produced were healthy and showed no signs of injury due to irradiation. However, the author cautions that the procedure is not entirely harmless and innocuous, in that with both methods, especially in women over 35 years of age, a permanent artificial menopause may be produced.

L. B. WINKELSTEIN

**Jarvis, Garth L.: Evaluation of Thyroid in the Treatment of Sterility, South M. J. 45: 1083, 1952.**

Thyroid treatment in the infertile couple has proved to be the only universally satisfactory procedure for infertility. Other forms of treatment, in the opinion of this author, have been disappointing.

Since it is believed that thyroid therapy predisposes to fertility through its ability to favor the development of a mature ovum, the author advocates its use. It is with the basal body temperatures that a correlation has been made between thyroid therapy and treatment of the infertile patient.

Those patients who have shown an inadequate progestational-phase endometrium generally have a low basal body temperature in the last half of their cycles. The administration of thyroid seems to favor the development of the progestational endometrium and therefore facilitates nidation and growth of the fertilized ovum.

Thyroid was administered by the author in a dose of 65 mg. daily to a group of patients suffering anovulatory cycles and others showing defective progestational changes in the endometrium. It was his belief that ovulation was induced in some patients and maturation of the endometrium was accomplished in others, thus favoring their fertility.

WILLIAM BICKERS

**Horne, Herbert W., Jr., and Rock, John: Oral Terramycin Therapy of Chronic Endocervicitis in Infertile Women, Fertil. & Steril. 3: 321, 1952.**

Fifty-six patients with long-standing infertility were given oral terramycin in an effort to clear the endocervix of bacteria which might be lethal to sperm. Medication was given on the sixth, fifth, and fourth days prior to ovulation (as determined by temperature curves). The dose was 3 Gm. of terramycin daily for one group and 6 Gm. daily for the second group.

No pregnancies occurred in the first group that could be attributed to the therapy (13 cases).

In the second group which received the higher dose there were 10 pregnancies in 35 patients, or 28 per cent, a figure somewhat higher than that expected by chance.

If the only recognized abnormality is poor or absent sperm migration, the authors state that "it seems reasonable to consider that terramycin given orally in 6 Gm. dosage for 3 days before ovulation improves the chance of conception."

EUGENE N. SCADRON

**Bender, S.: The End-Results in Primary Sterility, Brit. M. J. 2: 409, 1952.**

Bender reports an exhaustive study of 700 consecutive couples suffering from primary infertility. The youngest woman was 19 years of age and the oldest 43. Patients were traced for from three to seventeen years, regardless of the presence of absolute barriers to fertility. The over-all conception rate was 46.3 per cent, with 50 per cent of these becoming pregnant within six months of consultation and 64 per cent within twelve months of consultation. Two and one-tenth per cent were pregnant when first seen. The conception rate according to age was 52.3 per cent in patients under 30 years of age and 31.5 per cent in patients over 30 years of age. Proved genital tuberculosis occurred in 4 per cent of those who remained sterile.

Five hundred fifty-three of the 700 husbands had an analysis of semen, with 7.5 per cent showing azoospermia. Thirty-one per cent of the husbands of wives who conceived had counts below forty million per cubic centimeter. Of 57 men with repeated counts of below ten million per cubic centimeter, 19 were apparently successful in impregnating their wives, and of 16 men with sperm counts of less than one million, 4 were successful. The study showed little difference in male fertility when the count exceeded forty million per cubic centimeter.

The author estimates that at least half of the conceptions in the traced group were unrelated to medical treatment and suggests that some of this group may have become pregnant as the result of the psychological transference of the burden of infertility to the physician. The abortion rate was 21.8 per cent and the ectopic rate 1.7 per cent, both significantly higher than usually recorded. No increase in malformation rate in fetuses of more than 28 weeks' maturity was noted.

Treatment in the women consisted of dilatation of the cervix, endometrial biopsy, tubal insufflation, hysterosalpingography, and basal body temperature charts. The post-coital test, hormone therapy, and precoital douches were rarely employed. No low-dosage irradiation was administered.

All traced patients presented a history of from two to seventeen years' infertility at the time they were accepted for treatment. The author states that 77.4 per cent of all primigravidas on his obstetrical service became pregnant within one year of exposure. In view of this fact, he makes a plea for the lowering of the commonly set arbitrary two-year pretherapeutic trial period, and feels that one year of infertility is sufficient indication for therapy, particularly in patients who are in the latter decade of the childbearing period.

RANDOLPH GEPFERT

### Toxemia

**Hofbauer, J.: Progress vs. Perpetuation of Error Concerning the Origin of Pregnancy Toxemia, Am. J. Surg. 84: 394, 1952.**

The author traces the history of his thought on the etiology of pre-eclamptic toxemia. He discusses the importance of recent investigations of the basic vasopressor substance nor-adrenalin to an understanding of toxemia and restates his belief in overactivity of the pituitary-adrenal-pelvic chromaffin system and concomitant deficient function of the liver and placenta as fundamental mechanisms in its etiology. His "pelvic chromaffin system" may be of interest to readers unfamiliar with the author's study of Frankenhäuser's sympathetic ganglia and their growth and elaboration in pregnancy.

This report will not fail to be provocative.

S. B. GUSBERG

**Green, H. N., Hopewell, J. D., and Threlfall, C. J.: Plasma Pentose Levels in Pre-eclampsia and their Aetiological Significance, Brit. M. J. 2: 571, 1951.**

The authors, having originally studied the local and general effects of muscle ischemia, were prompted by the idea that perhaps overstretching of the uterine muscle might produce



a functional ischemia with the liberation of metabolites which could be interpreted as the exciting cause of the pre-eclamptic and eclamptic states. They have determined total and phosphorylated pentose levels in the blood of normal and toxemic patients and report a statistically significant increase in the content of both in toxemic patients. It is concluded that the rise in plasma pentose is evidence for reduced blood flow in the uterus and placental site of pre-eclamptic patients. They do not feel that peripheral vasoconstriction is the basis for the rise in pentose levels since this fact was not observed in hypertensive patients who do not have the true pregnancy toxemia. The convulsive state per se cannot be entirely responsible for the changes observed since high levels were observed in nonconvulsive cases. The authors finally review some of the evidence introduced to support the uteroplacental ischemia concept of Young and Page. They feel that the evidence of increased plasma pentose levels is more direct evidence to support the hypothesis.

DONALD G. JOHNSON

**Carey, H. M.: The Treatment of Pre-eclamptic Oedema With Ion Exchange Resins, J. Obst. & Gynaec. Brit. Emp. 59: 67, 1952.**

In patients who develop severe pre-eclampsia before the thirty-sixth week of pregnancy, it is desirable to employ treatment that will make it possible to continue the pregnancy for two or three weeks, until the infant is viable. At the Postgraduate Medical School, University of London, such patients on admission to the hospital are confined to bed and given a diet containing 700 to 800 mg. of sodium (2 Gm. salt) without restricting fluid intake. Each patient is weighed every day, and the albumin content of the early morning urine is determined, or, more recently, the total albumin excreted during each twenty-four hours has been determined. Blood pressure is recorded every four hours while the patient is awake. If the edema diminishes and the patient's clinical condition improves, this regime is continued until she can be delivered. In the early part of 1951, there were 4 patients who did not respond satisfactorily to this regime, who were treated with ion exchange resins; in 3 of these cases a mixture of the ammonium and the potassium resin in equal parts was used; in one, ammonium resin alone. Before this treatment was begun, the total body sodium was determined with the use of radioactive sodium; this was repeated a week later and again after delivery. Plasma sodium and potassium were estimated by the use of a flame photometer. The administration of the resins combined with low-sodium diet and high-fluid intake was found to reduce the edema of pre-eclampsia more rapidly than other methods of treatment. As the resin therapy in adequate dosages usually causes nausea in about a week it can then be temporarily discontinued and a diet rich in calcium given. Two of the 4 patients treated with the ion exchange resins were delivered spontaneously of living infants; one was delivered by cesarean section of a living infant; one was delivered of a hydropic infant by artificial induction of labor (rupture of the membranes). All these women are well with normal blood pressure and urine two months or more after delivery, indicating that the prolongation of pregnancy with this method of treatment involved no danger to the mother's health.

HARVEY B. MATTHEWS

**MacGillivray, I., and Govan, A. D. T.: Some Aspects of Renal Insufficiency in Obstetric Practice, J. Obst. & Gynaec. Brit. Emp. 59: 52, 1952.**

Ten cases of renal insufficiency in obstetric patients are reported; all these patients died, the average survival time being six and one-half days. The onset of the oliguria was preceded by hemorrhage, associated with toxemia, eclampsia, dystocia with sepsis, or hemorrhage of nontoxemic origin. In all patients except those who developed eclamptic convulsions, there was a phase of collapse or shock. In 2 cases, the temperature remained normal throughout the illness; in 4 cases the temperature was above normal throughout the illness, in 2 of which there was gross sepsis; in the other cases, there was a temporary rise in temperature. The renal lesions in these cases were similar to those described as lower nephron nephrosis. A

review of the clinical features in these cases shows that the predisposing factors and the clinical symptoms in lower nephron nephrosis and cortical necrosis are similar, except that a rise in temperature on the second or third day of oliguria is typical of cortical necrosis. In one of the cases, the pathological changes were those described as typical of lower nephron nephrosis, but in addition there was occasional thrombosis of a cortical arteriole. On the basis of these findings the authors suggest that the so-called lower nephron nephrosis is a milder degree of renal cortical necrosis, and that the term "renal insufficiency," rather than "lower nephron nephrosis" should be used to designate cases of this type, unless the rise in temperature typical of renal cortical necrosis develops on the second or third day of oliguria.

HARVEY B. MATTHEWS

### Tubal Insufflation

**Netto, A. Wolff, and Lerario, Domingos:** Tubal Permeability and Patency Determined by the Phenolsulfonphthalein Method, *An. clin. ginec. fac. med. Univ. São Paulo* 4: 157, 1950-1951.

The authors review all the methods of determining tubal permeability and patency with special emphasis on the P.S.P. method. The chemical and pharmacological properties of this product are reviewed. Fifty-two cases were investigated with this method and results checked later with tubal insufflation and hysterosalpingography.

P.S.P. is injected into the peritoneal cavity via the uterine and tube channels in the same fashion as carbon dioxide is injected in performing a Rubin Test. The coloring substance is absorbed through the peritoneum and its elimination is checked in the urine.

The authors conclude that: (1) The P.S.P. test is easy to perform, positive in its results, and very innocuous. (2) Results checked by tubal insufflation and hysterosalpingography were 100 per cent correct. (3) The test is considered positive when the P.S.P. can be recovered in the urine within one-half hour after injection. The velocity of excretion of P.S.P. injected in this fashion is one-third as fast as when the P.S.P. is injected intravenously.

RICARDO L. BORBEA

**Rubin, I. C.:** Comparison of Carbon Dioxide and Opaque Media in the Diagnosis of Tubal Patency, *Fertil. & Steril.* 3: 179, 1952.

The author discusses very clearly the comparative merits and the abuses of uterotubal insufflation and hysterosalpingography with emphasis on the use of carbon dioxide. In uterotubal insufflation CO<sub>2</sub> has become the gas of choice, because of its greater solubility, more rapid absorption, and less risk of producing embolism. The functional status of the Fallopian tubes, the presence of uterotubal spasm, and more especially of permeable tubal structures can be established by careful kymographic use.

In any diagnostic case CO<sub>2</sub> is more conveniently repeated and is less likely to provoke infection or pelvic pain. Following reconstructive tubal operations, it is safer and much more useful for the purpose of maintaining the patency of the new stoma.

Dangers encountered in the use of radiopaque media are outlined, namely: (1) possibility of producing occlusive foreign body granulomas in cases of tubal stricture; (2) intense pelvic pain; (3) pelvic infection due to persistent retention and chemical irritation.

In the diagnosis of intrauterine lesions by hystero-radiography radiopaque media should be limited to the smallest amount required to visualize the uterine cavity.

EDWARD C. HUGHES

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